National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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RIVM report 2022-0068
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N.A.H Janssen (author), RIVM
J. Hoekstra (author), RIVM
D. Houthuijs (author), RIVM
J. Jacobs (author), RIVM
A. Nicolaie (author), RIVM
M. Strak (author), RIVM

Contact:
Nicole AH Janssen
Duurzaamheid, Milieu en Gezondheid\Milieukwaliteit en Gezondheid
info@rivm.nl

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Synopsis

Effects of long-term exposure to ultrafine particles from aviation around Schiphol Airport

Health effects of long-term exposure to ultrafine particles from air traffic around Schiphol
Aircraft emit ultrafine particles. These are very fine particles in the air (smaller than 0.1 micrometre). People who live in the vicinity of Amsterdam Airport Schiphol are regularly exposed to higher concentrations of ultrafine particles from air traffic. RIVM has investigated the health effects of long-term exposure to ultrafine particles.

Long-term exposure to ultrafine particles emitted by air traffic may possibly have an effect on the cardiovascular system. For example, more people have started taking medication for heart disease in areas with high concentrations of ultrafine particles than in areas with low concentrations. Furthermore, exposure of pregnant women to ultrafine particles may possibly have a detrimental effect on the development of unborn children. We speak of possibly because there is too much uncertainty to conclude that there is a causal relation.

There are no indications that long-term exposure to ultrafine particles from air traffic is the cause of respiratory diseases. However, previous research has shown that short-term exposure can aggravate existing respiratory diseases. At the time, it was found that children suffered from more respiratory symptoms, such as shortness of breath and wheezing, on days with high concentrations of ultrafine particles.

In its latest study, RIVM examined the effects on the cardiovascular system, childbirth, the respiratory tract, the nervous system, diabetes and general health (including mortality). There is insufficient scientific evidence to suggest that exposure to ultrafine particles from air traffic has an impact on the nervous system or causes diabetes. ‘Insufficient evidence’ means that the results of the sub-studies of this study are either contradictory or unclear and that an insufficient number of other studies has been carried out. With the exception of a possible effect on death from arrhythmia, there are no indications that people die sooner if they are exposed to ultrafine particles from air traffic over many years.

This is the first time that such an extensive study has been carried out into the potential health effects of ultrafine particles from air traffic. The results reinforce previous conclusions reached by the Health Council of the Netherlands. As such, they increase the level of understanding of the possible effects of ultrafine particles on human health. To bolster these conclusions further, studies need to be carried out at other major international airports.

Keywords: UFP, aircraft, ultrafine particles, exposure, health, long-term exposure

Publiekssamenvatting

Gezondheidseffecten van langdurige blootstelling aan ultrafijn stof van vliegverkeer rond Schiphol

Vliegtuigen stoten ultrafijn stof uit. Dit zijn zeer kleine deeltjes fijnstof in de lucht (kleiner dan 0,1 micrometer). Mensen die in de buurt van Schiphol wonen staan regelmatig bloot aan hogere concentraties ultrafijn stof van vliegtuigen. Het RIVM heeft onderzocht wat de gezondheidseffecten zijn als mensen langere tijd ultrafijn stof inademen.

Langdurige blootstelling aan ultrafijn stof van vliegverkeer heeft mogelijk effect op het hart- en vaatstelsel. In gebieden met hoge concentraties zijn bijvoorbeeld meer mensen medicijnen tegen hartaandoeningen gaan gebruiken dan in gebieden met lage concentraties. Verder heeft blootstelling aan ultrafijn stof bij zwangeren mogelijk een nadelig effect op de ontwikkeling van ongeboren kinderen. We spreken van mogelijk omdat er te veel onzeker is om definitief te kunnen concluderen dat er een oorzakelijk verband is.

Er zijn geen aanwijzingen dat langdurige blootstelling aan ultrafijn stof van vliegverkeer de oorzaak is van aandoeningen aan de luchtwegen. Wel kan uit eerder onderzoek dat een korte blootstelling bestaande aandoeningen aan de luchtwegen verergeren. Toen bleek dat op dagen met hoge concentraties kinderen meer klachten hebben aan de luchtwegen, zoals kortademigheid en piepende ademhaling.

Het RIVM heeft in dit onderzoek gekeken naar effecten op: hart- en vaatstelsel, geboorte, luchtwegen, zenuwstelsel, diabetes en algemene gezondheid (waaronder sterfte). Er is niet genoeg wetenschappelijk bewijs dat blootstelling aan ultrafijn stof van vliegverkeer effect heeft op het zenuwstelsel of diabetes veroorzaakt. Niet genoeg bewijs betekent dat de resultaten van de deelonderzoeken van deze studie elkaar tegenspreken of niet duidelijk zijn. Ook zijn er weinig andere studies gedaan. Met uitzondering van een mogelijk effect op sterfte aan hartritmestoornis, zijn er geen aanwijzingen dat mensen eerder overlijden als zij jarenlang aan ultrafijn stof van vliegverkeer blootstaan.

Het is wereldwijd voor het eerst dat er zo'n uitgebreide studie is gedaan naar mogelijke gezondheidseffecten van ultrafijn stof van vliegtuigen. De resultaten versterken eerdere conclusies van de Gezondheidsraad en vergroten het inzicht in de mogelijke effecten van ultrafijn stof op de gezondheid. Onderzoek bij andere grote (internationale) vliegvelden is nodig om de conclusies verder te verstevigen.

Kernwoorden: UFP, vliegtuigen, ultrafijn stof, blootstelling, gezondheid, langetermijnblootstelling, kortetermijnblootstelling

Contents

Samenvatting

Onderzoeksprogramma gezondheidsrisico's ultrafijn stof rond Schiphol

Uit verkennend onderzoek naar de concentraties van ultrafijn stof rondom de luchthaven Schiphol bleek dat deze concentraties verhoogd zijn (Keuken et al, 2015; Bezemer et al, 2015). De betekenis hiervan voor de gezondheid van omwonenden is onduidelijk, omdat weinig bekend is over de gezondheidseffecten van UFP, in het bijzonder van vliegverkeer. Aanvullend onderzoek is nodig om beter inzicht te krijgen in de mate waarin UFP bijdraagt aan gezondheidseffecten (Bezemer et al, 2015; Janssen et al, 2016).

Het RIVM heeft van het ministerie van Infrastructuur en Waterstaat de opdracht gekregen om een integraal onderzoeksprogramma naar de gezondheidsrisico's van UFP rond Schiphol uit te voeren.

Het doel van dit meerjarig onderzoeksprogramma is inzicht te verkrijgen in de mogelijk nadelige gezondheidseffecten van ultrafijn stof rondom de luchthaven Schiphol. In het programma worden verschillende gezondheidsaspecten met verschillende studieopzetten onderzocht.

Het samenhangende meerjarige onderzoeksprogramma bestaat uit vier modules:

I. Onderzoek naar de langetermijnconcentraties ultrafijn stof van vliegverkeer in de omgeving van Schiphol (metingen & berekeningen).
II. Onderzoek naar de effecten van langdurige blootstelling aan ultrafijn stof van vliegverkeer.
III. Onderzoek naar gezondheidseffecten van kortdurende verhogingen van de concentratie van ultrafijn stof.
IV. Een module waarbinnen bovenstaande activiteiten worden geïntegreerd.

Dit rapport beschrijft het onderzoek naar de gezondheidseffecten van langdurige blootstelling aan ultrafijn stof van vliegverkeer (Module II).

De resultaten van modules I en III zijn in 2019 gerapporteerd (Voogt et al, 2019; Janssen et al, 2019).
In het vervolg van deze samenvatting wordt voor ultrafijn stof de afkorting UFP (*UltraFine Particles*) gebruikt.

Doelstelling en onderdelen

Het in dit rapport beschreven onderzoek richt zich op de volgende vraag:
Wat zijn de gezondheidseffecten van langdurige blootstelling aan UFP afkomstig van het vliegverkeer?

Om deze vraag te beantwoorden, zijn 4 deelstudies uitgevoerd onder volwassenen en/of kinderen uit 31 gemeenten rondom Schiphol:

1. Cohortonderzoek met sterftecijfers: een onderzoek waarin een groep mensen (cohort) gevolgd wordt in de tijd.
2. Onderzoek naar geboorte-uitkomsten (zoals laag geboortegewicht en vroeggeboorte).
3. Cohortonderzoek met medicijngebruik als maat voor specifieke aandoeningen: een onderzoek waarin het medicijngebruik van een groep mensen wordt gevolgd in de tijd.
4. Gezondheidsmonitor: Vragenlijstonderzoek naar gezondheid en leefstijlfactoren.

De eerste drie deelstudies zijn gedaan met bestaande gegevens in de registratie van het Centraal Bureau voor de Statistiek (CBS). Voor de vierde deelstudie is informatie gebruikt uit de reguliere Gezondheidsmonitor van GGD-en (Gezondheidsmonitor Volwassenen en Ouderen 2012 en 2016, GGD'en, CBS en RIVM). Er is gekeken naar data uit de periode 2006-2019 of een deel daarvan, afhankelijk van de deelstudie.

Hoofdconclusies

Er is onderzoek gedaan naar zes typen gezondheidseffecten: luchtwegaandoeningen (ademhalingsstelsel), hart- en vaatziekten (hartvaatstelsel), geboorte-uitkomsten, neurologische effecten (zenuwstelsel), metabole effecten (stofwisseling) en algemene gezondheid (waaronder totale sterfte). De hoofdconclusies voor deze soorten effecten zijn in onderstaande tabel samengevat. In het vervolg van deze samenvatting wordt dit nader toegelicht.

Tabel 1 Sterkte van de bewijslast voor risico van langdurige blootstelling aan UFP van vliegverkeer per type effect samengevat.

Type effect	**Sterkte bewijslast**
Luchtwegaandoeningen	Geen aanwijzingen
Hart- en vaatziekten	Indicatief bewijs
Geboorte-uitkomsten	Indicatief bewijs
Neurologische effecten (zenuwstelsel)	Onvoldoende bewijs
Metabole effecten (stofwisseling)	Onvoldoende bewijs
Algemene gezondheid[1]	Geen aanwijzingen

Samengevat concluderen we dat er indicatief bewijs is voor nadelige effecten van langdurige blootstelling aan ultrafijn stof van vliegverkeer op het hart- en vaatstelsel en geboorte-uitkomsten. Indicatief betekent dat er nog te veel onzeker is om definitief te kunnen concluderen dat er een oorzakelijk verband is. Er is onvoldoende bewijs voor effecten op het zenuwstelsel en de stofwisseling (diabetes). Dit betekent dat er onvoldoende informatie is om te beoordeling of er al dan niet sprake is van een verband. Er zijn geen aanwijzingen gevonden dat langdurige blootstelling aan ultrafijn stof van vliegverkeer luchtwegaandoeningen veroorzaakt of effect heeft op algemene gezondheid (totale sterfte, sterfte rondom de geboorte en ervaren gezondheid).

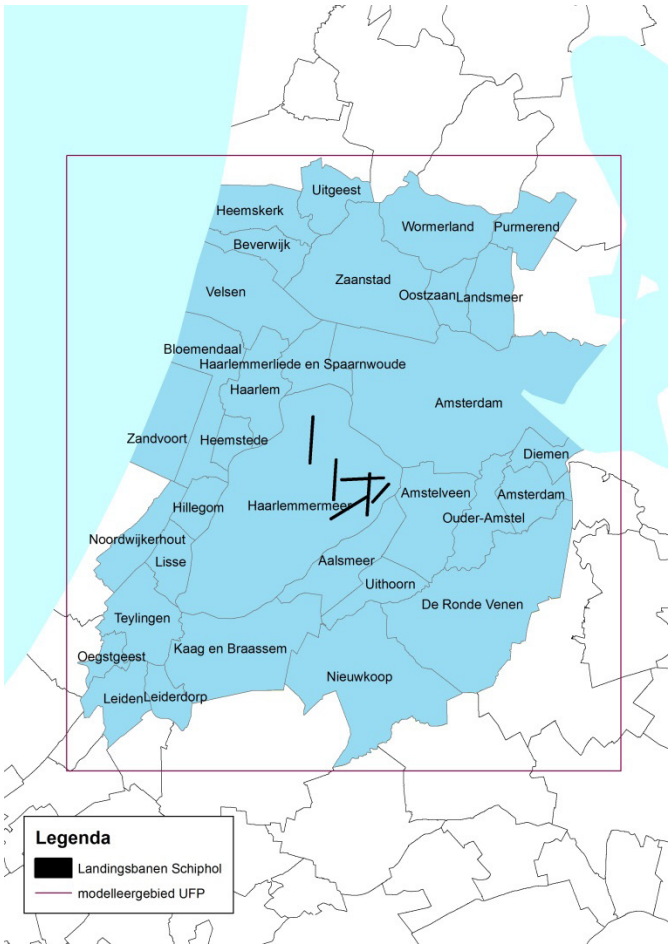
[1] Totale sterfte, sterfte rondom de geboorte en ervaren gezondheid.

Algemene opzet van de studies

Blootstelling en onderzoeksgebied
De blootstelling aan UFP van het vliegverkeer is met een rekenmodel geschat op alle woonadressen in een gebied van 50 bij 56 km rond Schiphol. Het rekenmodel is uitgebreid vergeleken met metingen op tien locaties rond Schiphol. Daaruit bleek dat het rekenmodel geschikt is voor de toepassing in de langetermijnstudies (zie Voogt et al, 2019).

De gemodelleerde blootstelling van inwoners op hun woonadres is gekoppeld aan gegevens over gezondheid uit registraties en vragenlijsten. Daarbij zijn alle woonadressen meegenomen uit gemeenten, die volledig in het gebied liggen waarvoor de blootstelling is gemodelleerd (zie figuur 1). Dit is gedaan voor de periode 2003-2019.

De gemiddelde jaarlijkse blootstelling aan UFP van vliegverkeer in de onderzoeksperiode op woonadressen was 1.890 deeltjes/cm^3, met duidelijk hogere blootstellingen nabij de luchthaven. Het verschil tussen woonadressen met de 5 procent laagste en 5 procent hoogste UFP-concentratie bedroeg ongeveer 3.500 deeltjes/cm^3. Dit is daarmee (ongeveer) de spreiding die in het onderzoeksgebied in blootstelling optreedt.



Figuur 1 Gemeenten in het studiegebied (op 1-1-2018) en het gebied waar UFP van vliegverkeer is gemodelleerd (50 bij 56 km).

Selectie van gezondheidsmaten
Binnen de verschillende registraties is informatie over een groot aantal mogelijke gezondheidseindpunten beschikbaar. Er is gekeken naar effecten op het ademhalingsstelsel (respiratoire effecten), effecten op hart- en vaatstelsel (cardiovasculaire effecten), metabole effecten, geboorte-uitkomsten, effecten op het zenuwstelsel, psychische gezondheid, en algemene gezondheid (waaronder sterfte).

Van tevoren is bepaald voor welke eindpunten de resultaten het zwaarst wegen in de interpretatie. Dit noemen we ***primaire*** eindpunten. Hiervoor zijn eindpunten geselecteerd die het meest zijn bestudeerd in relatie tot fijn stof en ook voor de deelstudies het meest betrouwbaar bepaald konden worden. De resultaten van de andere, **secundaire,** eindpunten zijn ondersteunend of verkennend gebruikt. In deze samenvatting noemen we de resultaten van de secundaire eindpunten alleen als er een verband is gevonden.

Verstorende variabelen
In de CBS-bestanden zijn gegevens beschikbaar over factoren die ook van invloed op gezondheid kunnen zijn, zoals leeftijd, geslacht, burgerlijke staat en inkomen. In de analyses is voor deze factoren gecorrigeerd.

Invloed van leefstijlfactoren
In de gebruikte registraties zijn geen gegevens beschikbaar over verschillende leefstijlfactoren (roken, alcohol, lichamelijke activiteit) en de Body-Mass-Index (BMI, een maat voor een gezond gewicht). De Gezondheidsmonitor bevat deze gegevens wel. Deze gegevens zijn gebruikt om inzicht te krijgen in de rol van die variabelen om zo de vraag te beantwoorden of er vertekeningen in de resultaten kunnen zitten, doordat we niet voor deze factoren konden corrigeren in de andere analyses. Deze invloed bleek beperkt.

Gevoeligheidsanalyses
In alle deelstudies is gekeken hoe robuust de resultaten zijn in een groot aantal gevoeligheidsanalyses. Hierbij is onder meer gekeken of de risicoschattingen beïnvloed worden door blootstelling aan andere luchtverontreinigende stoffen en aan geluid.

Beoordeling van de resultaten
Per deelstudie is voor elk individueel gezondheidseindpunt beoordeeld of er aanwijzingen waren voor een hoger risico bij hogere UFP-blootstelling. Als dat zo was, is de samenhang beoordeeld als een '*duidelijk verband'*, '*waarschijnlijk verband*' of '*mogelijk verband*'. Voor de overige gezondheidseindpunten is onderscheid gemaakt tussen '*geen verband*' en een '*omgekeerd verband'*. In de beoordeling is gekeken naar het patroon in de resultaten van het hoofdmodel en de gevoeligheidsanalyses.
De bevindingen zijn vervolgens samengevoegd per type effect (ademhalingsstelsel, hart- en vaatstelsel, metabool systeem, geboorte-uitkomsten, psychische gezondheid, zenuwstelsel en algemeen). Bij deze stap werd meer gewicht gegeven aan de primaire eindpunten.

De samenhang tussen de resultaten was dus belangrijker dan een op zichzelf staande statistisch significante bevinding.

Vertrouwelijkheid
De gegevens zijn voor het RIVM beschikbaar gesteld binnen een afgeschermde omgeving van het CBS. De externe gegevens over de blootstelling op het woonadres zijn voor het onderzoek in de afgeschermde omgeving gebracht. De koppeling met de persoonsgegevens is zodanig uitgevoerd, dat het RIVM individuele deelnemers niet kan herleiden.

De studies samengevat
Een aantal karakteristieken van de studies staat in tabel 3.

Tabel 3 Kort overzicht van de studies naar gezondheidseffecten van langdurige blootstelling van UFP aan vliegverkeer in 31 gemeentes rond Schiphol.

	Mortaliteit	**Medicijngebruik**	**Geboorte uitkomsten**	**Gezondheids-monitor**
Studie-opzet	Cohort	Cohort	Dwarsdoorsnede	Dwarsdoorsnede
Periode	2008 t/m 2019	2008 t/m 2019	2006 t/m2018	2012 en 2016
Populatie	Alle inwoners op 1-1-2008.	Alle inwoners op 1-1-2008, elk jaar (1-1) aangevuld met geborenen of nieuwe inwoners.	Alle geboorten waarvan de moeder ≥ 6 maanden van de zwangerschap in het studiegebied woonde (of de hele periode indien geboorte < 6 maanden).	Alle deelnemers die op 1 september van het enquêtejaar (2012 en 2016) in het onderzoeksgebied woonden.
Leeftijds-groepen	≥ 30 jaar (op 1-1 2008).	0-5 jaar, 6-14 jaar, 6-19 jaar, 12-19 jaar, ≥ 20 of 40 jaar[2].		Vanaf 18 jaar
Aantal deelnemers	1.259.591	Varieert per cohort (357.793-1.398.774).	285.809 geboorten	37.434 (2012) 55.074 (2016)

Mortaliteit

Bestudeerde eindpunten
In de studie naar mortaliteit is zowel totale sterfte (aan alle natuurlijke oorzaken) onderzocht als sterfte aan ziekten die mogelijk een verband hebben met blootstelling aan UFP (zie tabel 4).

[2] Afhankelijk van soort medicatie.

Tabel 4 Onderzochte doodsoorzaken. Links de primaire eindpunten, rechts de secundaire (grotendeels zijn dit subcategorieën van de primaire eindpunten, dan staan ze in dezelfde rij).

Primaire eindpunten **Sterfte aan:**	**Secundaire eindpunten** **Sterfte aan:**
Alle natuurlijke oorzaken samen	
Hart- en vaatziekten	Myocardinfarct Ischemische hartziekte (door vernauwing/verstopping van de kransslagaders) Hartritmestoornissen Cerebrovasculaire aandoening (beroerte, herseninfarct, hersenbloeding)
Luchtwegaandoeningen	COPD
Longkanker	
Zenuwstelsel	Dementie Alzheimer Parkinson
	Metabool: Diabetes

Opzet
Alle inwoners van het studiegebied op 1-1-2008, die op dat moment 30 jaar of ouder waren, zijn opgenomen in de studiepopulatie. Voor alle personen werd de langdurige blootstelling aan UFP bepaald door de jaarlijks gemiddelde UFP-concentratie op het woonadres toe te wijzen. Tot 1-1-2020 zijn de sterftecijfers (van het CBS) gevolgd in deze groep. Met statistische analyses is de relatie tussen de jaargemiddelde blootstelling aan UFP en de kans op sterfte bekeken.

Resultaten
Er werd bij de primaire eindpunten *geen verband* gevonden tussen de totale sterfte en sterfte aan verschillende ziekten en de blootstelling aan UFP van vliegverkeer. Uitzondering hierop was de sterfte aan neurodegeneratieve aandoeningen; die was lager bij hogere UFP-concentraties (*omgekeerd verband*). Er is niet goed te duiden waarom dit verband naar voren komt, ook omdat in de secundaire uitkomsten het verband met sterfte aan dementie en Alzheimer tegengesteld was.

Voor sterfte door hartritmestoornissen (een secundaire uitkomst) werd het verband met de jaargemiddelde UFP concentratie als *waarschijnlijk* beoordeeld.

Medicijngebruik

Bestudeerde eindpunten
Onderwerp van deze deelstudie was het starten met medicijnen (incidentie) voor aandoeningen van de luchtwegen, hart- en vaatstelsel, zenuwstelsel en metabole aandoeningen. Per medicijngroep is een aantal medicijnen geselecteerd. Ook is bepaald voor welke leeftijdsgroepen deze medicatie relevant is (zie tabel 5).

Tabel 5 Bestudeerde medicijngroepen en de bestudeerde leeftijdsgroepen.

Effect	Medicijngroep	Leeftijdsgroep
	Primaire eindpunten	
Luchtwegen	Astma COPD	0-5 jaar 6-19 jaar Vanaf 20 jaar
Hart- en vaatziekten	Hartaandoeningen	Vanaf 40 jaar
	Hoge bloeddruk	Vanaf 20 jaar
Stofwisseling	Diabetes	Vanaf 20 jaar
Zenuwstelsel	Parkinson	Vanaf 40 jaar

Effect	Medicijngroep	Leeftijdsgroep
	Secundaire eindpunten	
Zenuwstelsel	Dementie	Vanaf 40 jaar
Psychische klachten	Antidepressiva	12-19 jaar 20 jaar en ouder
	ADHD	6-14 jaar

Opzet
De studiepopulatie bestond uit elf groepen; per medicijngroep één of meer leeftijdscategorieën (zie tabel 5). Ze bestonden uit alle inwoners van die leeftijd in het studiegebied, en werden gevolgd in de gehele studieperiode (2008 t/m 2019). Mensen die in de twee jaar voorafgaand aan intrede in de studie[3] de betreffende medicijnen gebruikten, werden niet in de studie opgenomen. De jaarlijkse incidentie van de start met medicijnen werd gekoppeld aan de jaargemiddelde concentratie UFP door vliegverkeer op het woonadres.

Resultaten
Voor de primaire eindpunten werd een *waarschijnlijk verband* gevonden tussen de blootstelling aan UFP van vliegverkeer en start met medicijnen voor hartaandoeningen. Er werd *geen verband* gevonden met de start van medicijngebruik voor astma/COPD, hoge bloeddruk, diabetes of Parkinson.

Bij de secundaire eindpunten was er een *duidelijk verband* met medicijnen voor dementie: het risico hierop nam toe bij hogere concentraties UFP. Voor medicatie voor ADHD (6-14 jaar) en depressie onder jongeren (12-19 jaar) werd juist een *omgekeerd verband* gevonden (minder medicijngebruik bij hogere UFP concentratie).

Zwangerschap/geboorte uitkomsten

Bestudeerde eindpunten
Data over geboorte-uitkomsten zijn verkregen uit de database van de Perinatale Registratie Nederland (PRN) (zie tabel 6). Deze database bevat ongeveer 95 procent van alle geboorten in Nederland tijdens de studieperiode. De PRN-data zijn aangevuld met persoonlijke data van het CBS (over bijvoorbeeld leeftijd van de moeder, etniciteit, inkomen).

[3] Op 1 jan 2008 of op het moment dat ze in het studiegebied kwamen wonen of de betreffende leeftijd bereikten.

Tabel 6 Onderzochte geboorte-uitkomsten.

Primaire eindpunten	
Klein voor de zwangerschapsduur (SGA)	Geboortegewicht <10e percentiel op basis van geboortegewicht tabellen.
Laag geboortegewicht	Gewicht bij geboorte minder dan 2500 gram na ≥ 37 weken zwangerschap).
Vroeggeboorte	<37 weken 30-36 weken <30 weken

Secundaire eindpunten	
Sterfte	Sterfte rondom de geboorte (doodgeboorte en in eerste jaar).
Aangeboren afwijkingen	Per orgaansysteem
APGAR[4] score na 5 minuten	Laag (0-6), gemiddeld (7,8) en referentie (9,10).

Opzet
De studiepopulatie werd gevormd door een (administratief) cohort van alle moeder-en-kind-paren in het studiegebied, van wie het kind geboren werd tussen 1-1-2006 en 31-12-2018. De moeder moest minstens zes maanden van de zwangerschap in het studiegebied hebben gewoond (of de hele zwangerschapsduur als deze minder dan zes maanden betrof).

Voor de relatie met de blootstelling aan UFP is de blootstelling gedurende de hele zwangerschap meegenomen (op basis van de maandelijkse gemiddelden). Voor aangeboren afwijkingen is verder de concentratie tijdens de tweede maand van de zwangerschap gebruikt, omdat die het meest bepalend is voor aangeboren afwijkingen.

Resultaten
Bij de primaire eindpunten is er een *mogelijk verband* tussen blootstelling aan UFP van vliegverkeer tijdens de zwangerschap en vroeggeboorte en 'te klein bij geboorte voor de zwangerschapsduur'.
Voor laag geboortegewicht werd *geen verband* gevonden.
Bij de secundaire eindpunten werd het verband tussen de UFP-concentraties en aangeboren afwijkingen *waarschijnlijk* geacht.

Gezondheidsmonitor

Bestudeerde eindpunten
De primaire eindpunten 'slecht ervaren gezondheid' en 'ernstige psychische stress' (zie tabel 7) zijn alleen in deze deelstudie van het UFP-onderzoek beschikbaar. De data zijn afkomstig uit landelijke vragenlijsten (Gezondheidsmonitor 2012 en 2016).

[4] Een score die de verloskundige na de geboorte bepaalt door een aantal te scoren aspecten: Ademhaling, spierspanning, reflexen, huidskleur en hartslag.

De gegevens uit de Gezondheidsmonitor zijn ook gebruikt om nader te kijken naar medicijngebruik (als secundaire uitkomst). Dit is uitgevoerd om de bevindingen te ondersteunen uit de studie naar medicijngebruik. Een verschil is dat het hier gaat om de prevalentie van medicijngebruik (gebruik van medicijnen in het kalenderjaar van het invullen van de vragenlijst), en in de studie naar medicijngebruik over de incidentie (de eerste keer medicijnen gebruiken voor een bepaalde aandoening).

Tabel 7 Onderzochte eindpunten in de gezondheidsmonitor. Links de primaire eindpunten, rechts de secundaire eindpunten.

Primaire eindpunten	**Secundaire eindpunten**
Slecht ervaren gezondheid	
Ernstige psychische stress	
	Medicijngebruik voor Astma/COPD Antidepressiva Diabetes Hoge bloeddruk Hart- en vaatziekten *Aandoeningen* (waarvoor behandeld door een arts)[5] Diabetes Beroerte Hoge Bloeddruk Hartaanval Hartaandoening, anders Astma

Opzet
De studiepopulatie bestond uit alle inwoners uit het studiegebied die in 2012 of 2016 de Gezondheidsmonitor voor volwassenen (18-65) en ouderen (65+) hadden ingevuld. De Gezondheidsmonitor is een standaard vragenlijst die de GGD'en elke vier jaar afnemen onder een steekproef van de Nederlandse bevolking. Voor deze studie werden de data uit de vragenlijst gebruikt als de deelnemer in het jaar van de vragenlijst in het studiegebied woonde (en als bekend was waar diegene de vier jaar daaraan voorafgaand had gewoond).

Als blootstellingsmaat werd de jaargemiddelde UFP-concentratie door vliegverkeer berekend in het jaar voorafgaand aan de vragenlijst. Met statistische analyses werd gekeken naar de samenhang tussen die blootstelling aan UFP en de verschillende gezondheidsmaten.

Resultaten
Voor de primaire eindpunten (ervaren gezondheid en ernstige psychische stress) werd *geen verband* gevonden met de blootstelling aan UFP van vliegverkeer.

Een aantal secundaire eindpunten bleek wel *duidelijk* samen te hangen met hogere UFP-blootstelling: het voorkomen van diabetes, hoge

[5] Alleen voor 2012 beschikbaar.

bloeddruk (en het medicijngebruik voor beide aandoeningen) en het onder behandeling of controle zijn vanwege een hartaanval. Verder was er een *mogelijk verband* met een beroerte en het gebruik van medicijnen voor een hartaandoening.

Beoordeling per type effect

Sterkte bewijslast
Om een eindconclusie te trekken, zijn de bevindingen voor de afzonderlijke gezondheidseindpunten vervolgens samengevoegd per type effect (ademhalingsstelsel, hart- en vaatstelsel, geboorte-uitkomsten, zenuwstelsel & psychische gezondheid, stofwisseling en algemene gezondheid). Tabel 7.1 van het rapport geeft dit weer. In de beoordeling van de effecten zijn de primaire eindpunten, die we van tevoren hebben gedefinieerd, zwaarder meegewogen dan de secundaire eindpunten. De bevindingen zijn samen bekeken met de resultaten van de deelstudies naar acute blootstelling en de internationale literatuur. Ook het oordeel van de Gezondheidsraad uit 2021 over het bewijs voor effecten van UFP op de gezondheid is in ogenschouw genomen. Om aan te geven hoe sterk de bewijslast is voor een oorzakelijk verband tussen UFP-blootstelling van vliegverkeer en de verschillende gezondheidseffecten sluiten we ook aan bij de classificatie van de Gezondheidsraad (zie bijlage B). Hierbij maken we onderscheid tussen effecten die '*aangetoond*', '*waarschijnlijk*' of '*indicatief*' zijn, waarvoor de bewijslast '*onvoldoende*' is of waarvoor '*geen aanwijzingen*' zijn. Deze afwegingen leidden vervolgens tot de eindconclusies per type effect. De sterkte van de bewijslast is in tabel 8 samengevat; in de volgende paragraaf staat een toelichting op de classificatie.

Tabel 8 Sterkte van bewijslast voor risico van langdurige blootstelling aan UFP van vliegverkeer per type effect samengevat.

Type effect	**Sterkte bewijslast**
Luchtwegaandoeningen	Geen aanwijzingen
Hart- en vaatziekten	Indicatief bewijs
Geboorte-uitkomsten	Indicatief bewijs
Neurologische effecten	Onvoldoende bewijs
Stofwisseling	Onvoldoende bewijs
Algemene gezondheid	Geen aanwijzingen

Eindconclusies

Op grond van het onderzoeksprogramma en eerder onderzoek uit de internationale literatuur concluderen we dat *langdurige* blootstelling aan UFP van vliegverkeer mogelijk nadelige effecten heeft op het hart- en vaatstelsel en op geboorte-uitkomsten, dat er onvoldoende bewijs is voor effecten op diabetes, het zenuwstel en psychische klachten, en dat er geen aanwijzingen zijn voor effecten op het ademhalingsstelsel en algemene gezondheid. De conclusies en overwegingen per type gezondheidseffect zijn:

- **Hartvaatstelsel:** Er is *indicatief bewijs* dat langdurige blootstelling aan UFP van vliegverkeer leidt tot effecten op het hartvaatstelsel. Deze conclusie is gebaseerd op de resultaten uit de studie naar langdurige blootstelling aan UFP van vliegverkeer en wordt ondersteund door de resultaten uit het onderzoek naar gezondheidseffecten van kortdurende verhoogde blootstelling aan

UFP van vliegverkeer (Janssen et al, 2019). Daarnaast worden deze bevindingen ondersteund door andere studies naar de korte- en langetermijneffecten van UFP (algemeen).
- **Geboorte-uitkomsten**: Er is *indicatief bewijs* dat blootstelling aan UFP van vliegverkeer tijdens de zwangerschap een nadelige invloed heeft op geboorte-uitkomsten. Dit oordeel is gebaseerd op ons onderzoek en op resultaten van andere studies, waaronder een studie nabij het vliegveld van Los Angeles.
- **Ademhalingsstelsel**: Er zijn *geen aanwijzingen* gevonden dat langdurige blootstelling aan UFP aandoeningen van het ademhalingsstelsel veroorzaakt. Wel vonden we eerder dat kortdurende blootstelling aan hoge concentraties UFP bestaande luchtwegklachten kan verergeren en medicijngebruik voor deze aandoeningen kan verhogen (Janssen et al, 2019).
- **Stofwisseling (diabetes)**: Er is *onvoldoende bewijs* voor effecten van langdurige blootstelling aan UFP op het stofwisselingstelsel op basis van dit onderzoeksprogramma en de (beperkte) gegevens uit de wetenschappelijke literatuur.
- **Zenuwstelsel en psychische gezondheid**: Er is *onvoldoende bewijs* voor effecten van langdurige blootstelling aan UFP op neurodegeneratieve aandoeningen of op de psychische gezondheid is onvoldoende.
- **Algemene gezondheid**: Er zijn *geen aanwijzingen* gevonden voor een effect van langdurige blootstelling aan UFP van vliegverkeer op de totale sterfte[6], sterfte rondom de geboorte en ervaren gezondheid.

De gevonden verbanden bleven bestaan na correctie voor andere luchtverontreinigende stoffen (fijn stof, NO_2, roet) en geluid. Dit betekent dat de (mogelijke) effecten van UFP van vliegverkeer onafhankelijk zijn van (effecten van) blootstelling aan deze andere stoffen en geluid.

De bevindingen vergroten het inzicht in de mogelijke gezondheidseffecten van langdurige blootstelling aan UFP, in het bijzonder van vliegverkeer. Daarnaast versterken de bevindingen de eerdere conclusies van de Gezondheidsraad over de mogelijke gezondheidseffecten van UFP op het hart- en vaatstelsel en de groei en ontwikkeling van de foetus.

Aanbevelingen voor nader onderzoek

Alle studies in het onderzoeksprogramma zijn uitgevoerd bij één luchthaven (Schiphol). Gezien het indicatieve bewijs voor de effecten van UFP op het hartvaatstelsel en geboorte-uitkomsten, is verder vervolgonderzoek naar deze uitkomsten gerechtvaardigd.

Verder onderzoek zou het beste uitgevoerd kunnen worden bij (internationale) vliegvelden waar veel mensen zijn blootgesteld aan zowel hoge als lage UFP-concentraties. De zeggingskracht kan worden verhoogd door studies op dezelfde manier uit te voeren bij meerdere vliegvelden.

[6] Sterfte aan alle natuurlijke oorzaken samen.

Naast effecten op het hartvaatstelsel en geboorte-uitkomsten, zouden deze studies ook moeten kijken naar diabetes en dementie. Hoewel het bewijs voor de effecten van vliegverkeer op deze aandoeningen onvoldoende was, geven de bevindingen uit het Gezondheidsmonitor en studie naar medicijngebruik daarvoor aanleiding.

1 Introduction

1.1 Research programme on health effects of ultrafine particles around Schiphol Airport

Recent studies have shown elevated levels of ultrafine particles (UFP) in the vicinity of Amsterdam's Schiphol Airport (Keuken et al., 2015; Bezemer et al., 2015). The consequences for the health of local residents are unclear, because little is known about the health effects of ultrafine particles, in particular from aviation. Additional research is needed to gain a more precise insight into the extent to which exposure to ultrafine particles contributes to health effects (Bezemer et al., 2015; Janssen et al, 2016). The Ministry of Infrastructure and Water Management (formerly Ministry of Infrastructure and the Environment) commissioned RIVM to conduct an integrated research programme about the health risks of ultrafine particles around Schiphol Airport.

The multi-year research programme aims to gain insight into the possible adverse health effects of ultrafine particles around Schiphol Airport, by coherently studying and interpreting the possible risks from exposure to UFP from aviation for various health outcomes. Studying several health outcomes in different designs is important, because it enables an integral and coherent interpretation of the health effects (Janssen et al., 2016).

The multi-year research programme consists of four modules:

I. Research of the long-term concentrations of UFP from aviation in the vicinity of Schiphol Airport
II. Research of the health effects of long-term exposure to UFP from aviation
III. Research of the health effects of short-term increases in the concentration of UFP
IV. A module in which the above activities are integrated.

This report describes the research into the health effects of long-term exposure to UFP from aviation (Module II).

Research within this module focuses on UFP from aviation. Research on potential long-term effects of UFP from other sources (e.g. road traffic) requires a different approach. This is because road traffic is also a major source of other air pollutants, such as soot and NO_2, which makes it difficult to distinguish between the possible effects of UFP from road traffic and the effects of these other components.

Results of Module I and Module III have already been published (Voogt et al, 2019; Janssen et al, 2019). The integrated results and conclusions of the research programme as a whole will be described elsewhere.

1.2 Reading guide

Chapter 1 provides the background of the research programme and the position of the research presented in the current report in the programme as a whole. Chapter 2 describes the general design,

including the selection of health outcomes and the study area. Chapters 3 to 6 describe the different studies on mortality (chapter 3), pregnancy outcomes (chapter 4), medication use (chapter 5), and the public health monitor (chapter 6). Chapter 7 describes the overall discussion and conclusions.

2 General design

2.1 Objective and components

The research described in this report aims to answer the following research question:

What are the health effects of long-term exposure to UFP from aviation near Schiphol Airport?

We investigated effects of long-term exposure to UFP from aviation for a wide range of health outcomes and used data from existing health registries and surveys, available at the Central Bureau of Statistics (CBS). This includes data on mortality, pregnancy outcomes (e.g. low birth weight), medication use (as a measure of specific health conditions) and self-reported health problems. The survey data also provide information on lifestyle factors (such as smoking habits), which is not available in the other registries.

We investigated the relationship between long-term exposure to UFP from aviation and health by linking modelled concentrations of UFP from aviation at the residential address (Module I) to the existing health records and files.

We performed the studies on mortality, medication use and pregnancy outcomes with existing registrations, available at CBS.

For the questionnaire survey, we used the 2012 and 2016 national health survey (‘*Public Health Monitor Adults and Elderly of the Community Health Services, Statistics Netherlands and the National Institute for Public Health and the Environment, 2012 and 2016’)*. This is a standardised questionnaire survey among ~376,000 and ~450,000 adults, respectively, conducted by all municipal health services (GGD) in the Netherlands every four years, in collaboration with RIVM and CBS. In total, 93,408 of these subjects lived in the study area at the time of the questionnaire (see 2.4.2).

The different studies are described briefly below, and in detail in the separate chapters (chapters 3 to 6).

2.2 Summary of the different study designs

2.2.1 General aspects

2.2.1.1 Study period

Schiphol Airport expanded in 2003 with a new runway which influenced the spatial distribution of the exposure to UFP from aviation. It is important to start the studies of the long-term exposure of UFP a few years after the introduction of the new runway. This way, we can avoid (large) spatial changes and uncertainties in UFP exposure in the study population near the new runway just before their entrance in a health study. We used an (arbitrary) period of 5 years, resulting in a follow-up period in the cohort studies on mortality and medication use from 1-1-2008 until 31-12-2019 (12 years). For pregnancy outcomes and self-

reported health no restriction based on the opening of the new runway was needed. Self-reported health data was available for 2012 and 2016. The exposure for the birth outcome study was considered from 3 months before pregnancy until birth, and data was available from 2004-2018. As for the years 2004 and 2005 more than 50% of the information on maternal education was missing, the study period was set to births from 1-1-2006 until 31-12-2018.

2.2.1.2 Study area

The study area consists of the municipalities that are fully included in the modelling area of UFP from aviation for 50 by 56 km around Schiphol Airport at January 1 2018. The rationale for the choice is given in section 2.4.2.

Figure 2.1 shows the 31 municipalities and the modelling area. In total, over 2.2 million residents lived in the study area on 1-1-2018.

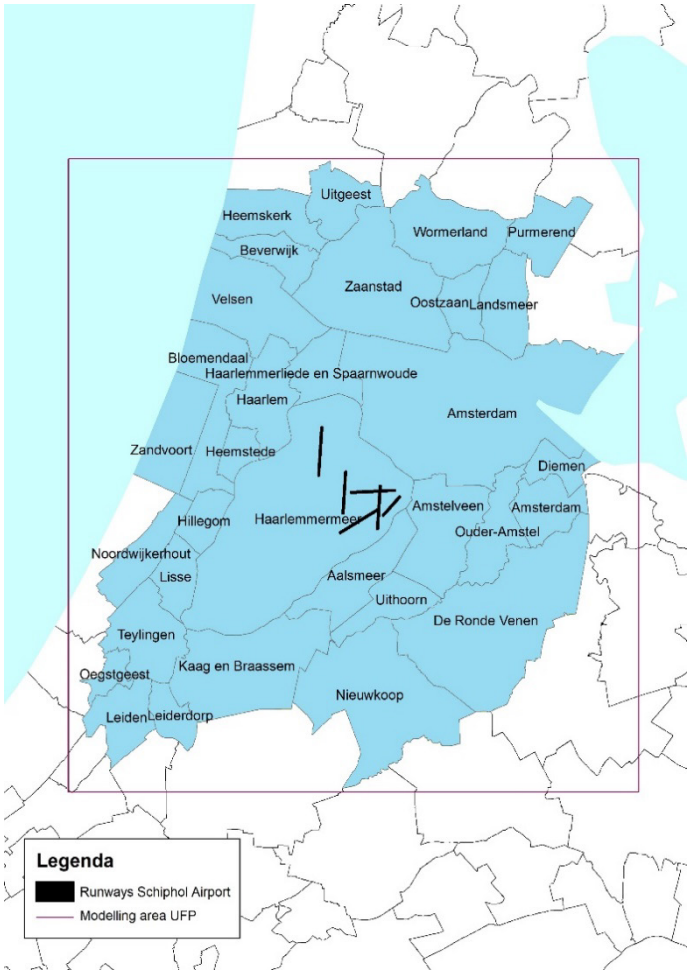


Figure 2.1 Municipalities (at 1-1-2018) in the study area and modelling area of UFP from aviation (50 by 56 km).

2.2.2 Mortality

We studied the association between long-term exposure to UFP from aviation and natural and cause-specific mortality (see paragraph 2.3.2 and table 2.3) in an administrative cohort that includes all residents

aged 30 years and older in the study area, on 1-1-2008. The cohort was compiled based on data from several databases at CBS, including the longitudinal mortality registry for follow-up, individual covariates (such as sex, marital status, region of origin and standardised household income) and area-level socio-economic status covariates (e.g., mean income, education or unemployment rate). The follow-up period for the cohort was from 1-1-2008 to 1-1-2020 (12 years). We excluded subjects with missing data on residential history or exposure in the five years before baseline and excluded subjects who had a primary address outside the study area in 2007. We used Cox-proportional hazards regression models with age as underlying time scale, stratified by sex and adjusted to individual and area-level confounders (see paragraph 2.6 and table 2.6). We used time-varying exposure analyses to account for residential history and time trends in exposure and (cause-specific) mortality during follow-up. For each year of follow-up, we linked the corresponding annual average exposure to UFP from aviation for the residential address with the longest duration of residence in the preceding year. We evaluated the shape of the exposure-response curves by using natural splines with 3 degrees of freedom. We also performed a number of sensitivity analyses to investigate the robustness of the results, including adjustment other air pollutants and noise (see paragraph 2.10 and table 2.8).

2.2.3 Dispensing of medication

We studied the association between the incidence of specific medication groups for various age groups (see paragraph 2.3.2 and table 2.3) over the period 2008-2019 and the long-term, time-varying, exposure to UFP from aviation, accounting for individual-level determinants and socio-economic indicators measured on neighbourhood level. Individual data on the dispensing of medication covered by the basic health insurance package was available per calendar year for the period 2006-2019 from the National Health Care Institute and was linked to data from several databases from CBS (see above). Information about the prevalence of the medication group in the two previous calendar years was used to assess the incidence in a calendar year, (see 5.2.2). The administrative cohort included all residents on 1-1-2008 and all new-borns and new residents on first of January of subsequent calendar years in the study area: the baseline year of the cohort members is variable. Entry in the cohort after 1-1-2008 was allowed to maximize the number of young children. Since medication prescription practice may vary between family doctors, and information on the family doctor was not available, we used district (in Dutch: "wijk") as surrogate assuming that the choice of the family doctor is based on the location of the residential address. We excluded subjects who used the medication from the specific medication group in any of the two calendar years before baseline, subjects with missing data on residential history or exposure in the five years before baseline, subjects that did not live in the two years before baseline in the same district as in the first calendar year of the study, and subjects that lived in any of the two years before baseline or in the first calendar year of the study more than 275 days in an institution (since dispensing of medication may in this situation not be registered in the basic health insurance). For children less than two years old at baseline the above mentioned criteria on duration were replaced by the criterion from birth. We used Cox-proportional hazards regression

models with age as underlying time scale, stratified by periods of three years to adjust for time trends and adjusted for individual and area-level confounders (see paragraph 2.6 and table 2.6). The analyses were carried out separately for men and women. The covariates were registered once a year at 1-1 (e.g. age) or refer to the situation for a whole calendar year (e.g. household income). We censored subjects at 31-12 of the concerning calendar year in case of: first time use of medication of the specific medication group, deceased in the concerning calendar year or at 31-12-2019 (end of study). We censored subjects at 31-12 of the preceding calendar year in case of: no longer fulfilling the criterium for the age group on the first of January, the residential address with the longest duration in the calendar year is outside the study area or living more than 275 days in an institution in the concerning calendar year. The registered reason for censoring refers to the event that occurred at first. We used district as random effect in the statistical analyses (Cox shared frailty model). For other aspects of the statistical analyses we refer to the design of the mortality study.

2.2.4 Pregnancy outcomes

In this part we evaluated associations between exposure to UFP from aviation at the residential address of the mother during pregnancy and pregnancy outcomes over the period 2006-2018. Information on pregnancy and birth from the Perinatal Registration Netherlands (PRN) was obtained from Perined (www.perined.nl) and linked to registry data on individual level and indicators of socio-economic status on area level from CBS. We identified birth records from mothers that lived in the Schiphol area for at least 6 months during pregnancy. We excluded birth records with less than 22 weeks (154 days) of pregnancy because a large number of records in this group had no personal identification number, so these records could not be enriched with information from other data sources. Other exclusion criteria included non-singleton pregnancies, records from mothers younger than 16 years of age at birth, mothers with incomplete address history during pregnancy and mothers who changed addresses more than once during pregnancy. We assessed associations between exposure to UFP from aviation during pregnancy and pregnancy outcomes with logistic regression models. We used multiple imputation by chained equations (MICE) to impute missing covariates. We used splines with 3 degrees of freedom to explore the linearity of associations between pollutants and health outcomes. We performed sensitivity and stratified analyses to study whether associations between UFP and pregnancy outcomes differ in certain subgroups and whether the findings from the main model were robust. An overview of the study specific health outcomes, exposure specification, statistical methods/confoundermodels and performed sensitivity/stratified analyses, can be found elsewhere (table 2.3, 2.4, 2.6 and 2.8).

2.2.5 Public health monitor

We used cross-sectional data from two national health surveys (Public Health Monitor 2012 and 2016, PHM (*'Gezondheidsmonitor Volwassenen GGD-en, CBS en RIVM'*) to study the association between long-term exposure to UFP from aviation and self-reported health and medication use prevalence (see paragraph 2.3.2 and table 2.3). The PHM is a standardised questionnaire survey among ~376,000 and ~450,000

adults (aged ≥ 19 years) respectively, conducted by all municipal health services (GGD) in the Netherlands every four years, in collaboration with RIVM and CBS. The PHM covers issues related to personal characteristics, lifestyle, socio-economic status and physical and mental health. We selected all inhabitants who lived within the study area on the first of September[7] of the year of the survey (2012 or 2016) and from whom we had complete information on residential history in the year of the survey as well as the 4 years before the survey (i.e. 2008-2012 or 2012-2016). We excluded subjects off whom the primary address in the year of the survey was outside the study area. We used multiple imputation by chained equations (MICE) to impute missing values for individual covariates. We excluded subjects who had more than one missing value off the variables smoking status, alcohol use, physical activity and BMI (2,529 subjects; see 6.2.6.1), resulting in a study population of 36,617 adults in 2012 and 54,263 in 2016. We used logistic regression models, adjusting for individual and area-level confounders (see paragraph 2.6 and table 2.6). We evaluated the shape of the exposure-response curves by using natural splines with 3 degrees of freedom and performed a number of sensitivity analyses to investigate the robustness of the results, including adjustment for other air pollutants and noise.

The PHM includes information on lifestyle factors (e.g. smoking, alcohol use, BMI and physical activity), which is not available in the other registries. We therefore also used the PHM to gain insight into potential residual confounding by incomplete adjustment for these factors in the other sub-studies. This includes indirect adjustment of associations with mortality and evaluation of the effect of adjustment for these factors on the association between UFP from aviation and prevalence of medication use for medication groups included in the study on incidence of these medication groups (see paragraph 2.12).

2.2.6 Overview of the different studies

The general design of the 4 studies is summarised in table 2.1.

[7] The surveys were carried out in de period September-December. A fixed survey date of September 1 is used for all data linkages.

Table 2.1 Overview of the populations included in the different studies.

	Mortality	Medication use	Health monitor	Pregnancy outcomes
Study design	Cohort study	Cohort study	Cross-sectional study	Cross-sectional study
Study period	Follow-up from 1-1-2008 until 31-12-2019.	Follow-up from 1-1-2008 until 31-12-2019 .	2012 + 2016	All singleton live[1] births between 1-1-2006[2] and 31-12-2018.
Population – study area	All residents who lived in the study area at 1-1-2008.	All residents, who lived in the study area at 1-1-2008 and new-borns and new residents every first of January of subsequent years.	All participants who lived in the study area on 1 September of the year that the questionnaire was filled out.	All births off which the mothers lived in the study area and were at least six months pregnant, or carried for the full pregnancy period in case of a pregnancy between 22 and 26 weeks.
Population: age inclusion criteria	Age ≥30 on 1-1-2008 (no new entries after that).	Different age groups: 0-5 yr, 6-14 yr, 6-19 yr, 12-19 yr and 20 or 40 years and older (depending on the health outcome).	All participants.	Pregnant for ≥22 weeks Maternal age at birth > 16 year.
Addition exclusion or inclusion criteria based on residential history	Exclude subjects of whom we had incomplete information on residential history or exposure in the 5 years before baseline. Exclude subjects for whom the primary	Exclude subjects of whom we had incomplete information on residential history or exposure in the 5 years before baseline. Lived at least two years or, for children younger than two years of age, lived from birth in the same district in the study area.	Exclude subjects of whom we had incomplete information on residential history or exposure in the year of the survey and the 4 years before the survey took place.	Exclude mothers with incomplete residential history during pregnancy. Exclude mothers who changed address more than once during pregnancy.

	Mortality	Medication use	Health monitor	Pregnancy outcomes
	2007 address is outside the study area.	Lived in a private household (no institution)[3] Did not use medication belonging to the ATC medication groups of interest in the last 2 years BEFORE entering the study. When moving into the study area, a person did not previously live within the study area starting from 1 January 2008.	Exclude subjects off whom the primary address in the year of the survey was outside the study area.	
Number of subjects	1,259,591 (13,603,814 person-years)	11 populations, ranging from ~350,000 for asthma in 0-5 year olds to ~1,400,00 for diabetes; see chapter 5.	36,617 (2012) + 54,263 (2016)	285,809 live births.

[1] Except for analyses on stillbirths, infant mortality and congenital anomalies (secondary health endpoints).
[2] Data from 2004-2005 were excluded on forehand because of high frequency (>50%) of missing information on maternal education.
[3] Medication use in some types of institutions is not recorded in the basic health insurance.

2.3 Selection of health outcomes

2.3.1 Introduction

The selection of health outcomes is preferably based on and guided by what scientific literature describes as most likely outcomes to be associated with long-term exposure to UFP. The report of Bezemer et al. (2015) gives an overview of the state of the art of toxicological and epidemiological evidence of the health effects of exposure to ambient UFP. By the time the report was published,, four extensive literature studies were available in which all studies between 2000 – 2009 were described and evaluated (EPA, 2009; Knol et al, 2009; HEI, 2013, WHO, 2013). At that time, no studies were available on the health effects of long-term exposure to UFP from aviation or from other sources.

At the start of the study, two recent reviews were available that included studies on health effects of long-term exposure to ambient UFP: the EPA Integrated Science Assessment (ISA) for Particulate matter (US EPA, 2019) and the report Health Effects of Ultrafine Particles of the German Umwelt Bundesamt, 2018 (UBA, 2018; Ohlwein et al., 2019).

Overall, there was increasingly suggestive evidence for independent short-term health effects, but the evidence remained largely inadequate to draw firm conclusions on long-term effects of UFP. EPA identified one health effect in relation to long-term exposure to UFP as "suggestive of, but not sufficient to infer", i.e. effects on the nervous system (see table 2.2). This is based on animal toxicological studies and supported by one epidemiological study on cognitive outcomes among school children.

Table 2.2 Causality determinant for UFP based on ISA 2019 (US EPA, 2019).

Health outcome	Short term	Long term
Respiratory	Suggestive of, but not sufficient to infer	Inadequate to infer
Cardiovascular	Suggestive of, but not sufficient to infer	Inadequate to infer
Metabolic effects	Inadequate to infer	Inadequate to infer
Nervous system	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
Pregnancy outcomes		Inadequate to infer
Cancer		Inadequate to infer
Mortality	Inadequate to infer	Inadequate to infer

In comparison, for PM2.5 EPA classified all outcomes as likely to be causal or causal, with the exception of metabolic effects and pregnancy outcomes (which were classified as "suggestive of, but not sufficient to infer").

In the German review, several outcomes were identified in recent literature that showed increasingly suggestive evidence for independent short-term health effects on inflammation, autonomic tone and blood pressure. For long-term health effects no such outcomes were identified.

At the start of this study, no studies were published that assessed the health effects of UFP from aviation on health of residents living around

airports. In 2020, a study was published that showed an association between UFPs from aviation and preterm birth among pregnant mothers living downwind of Los Angeles International Airport (LAX) (Wing et al, 2020). This supports the inclusion of this outcome.

Taken the two recent reviews and the previous reviews together, we therefore concluded that, at the moment, there was no scientific basis to include or exclude specific outcomes in a study on the health effects of long-term exposure to UFP from aviation around Schiphol Airport.

We therefore based the selection of health outcomes on the list of health outcomes evaluated for particulate matter in general: respiratory outcomes, cardiovascular outcomes, metabolic effects, nervous system, mental health, pregnancy outcomes, cancer and mortality (as in table 2.2).

2.3.2 Health outcomes

We used health data from existing registries and surveys, available at the Central Bureau of Statistics (CBS). Within these different datasets a large number of possible health endpoints is available. Including all health endpoints would result in multiple testing issues. We therefore distinguish between primary and secondary endpoints. As primary endpoints we included endpoints that have been most widely studied in relation to fine particles. Results of the primary endpoints are considered as hypothesis testing while results of the secondary endpoints are considered as hypothesis generating and as supporting to the primary outcomes. In the overall interpretation of the results, the focus will be on the primary endpoints.

For cause-specific **mortality**, we selected the broad groups as primary endpoints and included more specific causes of death as secondary endpoints. Primary endpoints were mortality due to natural causes, cardiovascular disease, respiratory disease, lung cancer and neurodegenerative disease. Neurodegenerative disease mortality included dementia, Parkinson's disease, Alzheimer's disease and multiple sclerosis, as in a recent Dutch nationwide study on the combined effects of air pollution, noise and green space (Klompmaker et al, 2020). As secondary endpoints we included specific causes of death that were also included in the ELAPSE study (Effects of Low level Air Pollution: a Study in Europe) (Brunekreef et al, 2021). In addition, we included arrhythmia in relation to the finding of a prolonged QTc interval in relation to short-term exposure to UFP in the volunteer study (Janssen et al, 2019; Lammers et al 2020). We also included dementia and Alzheimer's disease as secondary endpoints, as these are the most prevalent specific causes of death within the neurodegenerative disease endpoint.

For **medication use**, we used information about the reimbursement of medication covered by the basic health insurance package. Since 2006, health insurers provide yearly information to the National Health Care Institute (Zorginstituut Nederland) for the so-called risk equalisation. The risk equalisation compensates health insurers for differences in the composition of their insured population. Information about the number of patients with certain chronic diseases is used among other things for

the risk equalisation. These patients are identified on the basis of claims for medicines that are known to be prescribed for the disorder in question (pharmacy cost groups). Some of these pharmacy cost groups are related to the health outcomes of interest in table 2.2. We used groups of mediation dispensed for asthma/COPD, for heart disease, for hypertension, for diabetes I and/or diabetes II, and for Parkinson's disease as primary endpoints, and groups of mediation dispensed for depression, for dementia syndromes and for ADHD as secondary endpoints. Medicines are internationally classified according to the Anatomical Therapeutic Chemical Classification with defined daily doses (ATC/DDD system). Pharmacy cost groups are based on 7-digit ATC codes. The medication covered by the basic health insurance package is only in an aggregated form available for research at CBS. We defined the medication groups on the basis of 4-digit ATC codes approximating the pharmacy cost groups. The codes for the medication groups are provided in table 2.3. For asthma/COPD, distinguished between children aged 0 to 5 years, between children and adolescents aged 6 to 20 years and persons aged 20 years and older, since the Dutch College of General Practitioners distinguishes in their guideline for asthma in children between children up to six years of age and children over six years of age. Adults may be affected by other risk factors such as smoking habits and occupational exposure to air pollution. For ADHD and depression among children and adolescents, we initially selected the same age group as for asthma/COPD, but based on information about the incidence, we changed the age category to 6-14 years for ADHD and to 12-19 years old for anti-depressants. For medication for hypertension, for diabetes and for depression, we selected adults aged 20 and older; for medication for heart disease, for Parkinson's diseases and for dementia syndromes the population under study was 40 years and older. Medication use for these conditions at a younger age is rare.

For **pregnancy outcomes,** we included low birth weight (LBW), small for gestational age (SGA) and preterm birth as primary endpoints as these are most widely studied in relation to air pollution. Mortality before the age of 1, including stillbirth, congenital anomalies and low Apgar scores (as indicator of longer-term reduced cognitive development (Odd et al. 2007, Ehrenstein et al. 2009, Razaz et al. 2015) were included as secondary endpoints as the available evidence for these outcomes is more limited.

For the **health monitor**, we included self-reported perceived health and psychological distress as primary endpoints, as these endpoints are not available in any of the other registries. In the overall interpretation of the results, however, we will put less weight on these endpoints compared to the other primary endpoints, for which there is more evidence of effects of particulate matter in general. The other self-reported health outcomes (only available for 2012) were included as secondary endpoints and are mainly used to support results of similar outcomes in the other registries. In addition, data from the health monitor is used to provide insight into the extent to which relationships between exposure and health can be confounded by incomplete adjustments to lifestyle factors. Paragraph 2.11 describes this.

Table 2.3 provides an overview of the primary and secondary health endpoints included in the different studies.

Mortality, respiratory and cardiovascular outcomes and effects on the metabolic and nervous systems and mental health among adults seem to be adequately covered by the existing registration systems.

Cancer is limited to mortality due to lung cancer. Information on cancer incidence was not available for use in the project. We explored the use of mortality for other specific cancers as secondary endpoints but decided to not pursue this because of high survivability and/or low numbers of cases for most other types of specific cancers.

Postnatal effects on *children* (other than infant mortality in the first year of life) are only included in the study on medication use, and only include respiratory effects as primary outcomes; for nervous system effects of use of anti-depressants and ADHD medication are included as secondary outcomes. There is evidence that UFP exposure in the brain can lead to inflammatory responses; these reactions may aggravate neurodegenerative diseases and affect brain morphology and release of neurotransmitters that affect memory and behaviour (Heusinkveld et al., 2016). There is one epidemiological study that looked into the effects of UFP on cognition: Sunyer et al. (2015) studied the association between UFP and cognitive growth in schoolchildren. We commissioned IRAS (Utrecht University) to explore the feasibility of studying these effects in the ABCD – Amsterdam Born Children and their Development – cohort. The conclusion was that most of the outcomes linked to child development would most likely have too low statistical power to analyse outcomes using ABCD as a stand-alone study. We also considered the re-use of data on cognition collected among children at 24 primary schools in the vicinity of Schiphol in the framework of the RANCH study (van Kempen et al., 2005; van Kempen et al., 2012). This idea was discarded because it is likely that the exposure estimates from the current UFP model deviate too much from the exposure at the time of the study; the fieldwork at the schools was carried out in 2002 and this was before the expansion of Schiphol Airport with an additional runway in 2003.

Table 2.3 Overview of the health endpoints included in the different studies.

	Mortality	**Medication use[1]**	**Health monitor**	**Pregnancy outcomes**
Primary health endpoints	- Natural (ICD A00-R99) - Cardiovascular (I10-I70) - Respiratory (J00-J99) - Lung cancer (C34) - Nervous system (F00-F03; G20-G22; G30; G35)	- Diabetes type I and/or diabetes type II (ATC A10A; A10B): 20 years and older - Chronic Non-Specific Lung Disease (ATC R03A-RO3D): 0-5 years, 6-19 years, 20 years and older - Heart diseases (ATC C01A-C01E; C03C): 40 years and older - Hypertension (ATC C02A,C,D,K; C03A,B,D,E; C07A,B,C,F; C08C,D,G; C09A,B,C,D,X): 20 years and older - Parkinson's disease (ATC N04B): 40 years and older	- Poor self-reported health (poorest 2 in 5-point scale) - Psychological distress (>30 in Kessler Psychological Distress scale (K10))	- Birth weight (gram) - low birth weight (<2500 gr) - Gestational age (weeks) - prematurity (< 37 weeks) - severe prem. (< 30 weeks) - moderate prem. (30-36 w) - Small for gestational age (birth weight below the 10th percentile adj. for sex and gestational age)
Secondary health endpoints	- Ischemic heart disease (ICD I20-I25)- Myocardial infarction (I21-I22) - Arrhythmia (I46-I49) - Cerebrovascular (I60-I69) - Stroke (I60-I64) - Diabetes (E10-E14) - COPD (J40-J44, J47) - Dementia (F00-F03) - Alzheimer's disease (G30) - Parkinson's disease (G20-G22)	- Dementia syndromes (ATC N06D): 40 years and older - Anti-depressants (ATC N06A): 12-19 yrs, 20 years and older - ADHD (ATC N06B): 6-14 yrs	**2012 only:** Self-reported diabetes Self-reported high blood pressure Self-reported stroke Self-reported heart attack Self-reported other heart diseases Self-rep. asthma/COPD Natural cause mortality[2] **2012+2016:** Medication use (prevalence) for diabetes, hypertension, heart disease, depression, asthma/COPD	Infant mortality; <1 year of age (including stillbirth) Low Apgar scores Congenital anomalies - Nervous and senses system - Circulatory system - Respiratory system - Digestive system - Urogenital system - Musculoskeletal system - Skin and abdominal wall - Any of the above

[1] See paragraph 2.4.2 for the age groups in which the different endpoints are studied.
[2] See paragraph 2.12 on use of the health monitor data to gain insight into residual confounding by incomplete adjustment for lifestyle factors.

2.4 Study area

2.4.1 Introduction

Section 2.2.1.2 describes the study area. Section 2.4.2. gives the rational for the choice.

2.4.2 Rationale

In a previous study, 21 municipalities were selected of which part of their territory was within 10 km distance of one of the runways. The population consisted of 1.7 million residents (January 1, 2004) (Janssen et al, 2016). At that time, preliminary results were available on the concentration UFP from aviation in a modelling area of 25 by 35 km. The 3,000 #/cm^3 contour and contours of higher concentrations were fully closed in this modelling area. Thirty nine percent of the population lived within the 3,000 #/cm^3 contour. For lower concentrations, the exposure assessment became more uncertain since part of the study population lived outside the modelling area. Based on the exposure distribution in the population, we estimated that a follow-up period of about 12 years was necessary to detect with a power of 0.80 a hazard ratio of 1.003 per 1,000 #/cm^3 (Janssen et al, 2016). The hazard ratio of 1.003 per 1,000 #/cm^3 for mortality in relation to long-term exposure to UFP was estimated in an expert elicitation study (Hoek et al., 2010). The estimated risk had a 90% confidence interval from 1.001 to 1.009 per 1,000 #/cm^3.

For this study, we decided to enlarge the modelling area to improve the exposure characterisation below 3,000 #/cm^3, which contributes to the exposure contrast in the study area. The enlargement only leads to more people in the lower exposure categories and does not increase the size of the population in the high exposure classes.

We extended the previous modelling area for UFP in northern direction (up to Uitgeest) to include all municipalities served by the Community health service Kennemerland and in eastern direction to include the full territory of the Community health service Amsterdam. Furthermore, we extended the previous modelling area in southern direction to include all residential addresses in Nieuwkoop, a municipality that was already part of the study area in Janssen et al. (2016) to avoid uncertainties in the UFP exposure at lower levels. Lastly, we extended the area in western direction to keep Schiphol Airport in the middle of the modelling area. The final demarcation was based on the choice to include a relatively large municipality (Leiden) in the southwest part of the study area.

We selected only residents in municipalities that are fully included in the new modelling area of 50 to 56 km. This is because we could use municipality as administrative level in our statistical analyses (see 2.8.3.2).

2.5 Exposure to UFP from aviation

2.5.1 Introduction

We estimated exposure to UFP from aviation using the dispersion model as evaluated in Module I of the research program (research into the long-term concentrations of ultrafine particles from aviation around Schiphol Airport), as described by Voogt et al (2019). We used the

model to estimate monthly average concentrations of UFP from aviation at all residential addresses in the modelling area (50*55 km), for the period 2003-2019.

2.5.2 Model

Briefly, hourly UFP concentrations from aircraft emissions were calculated for grid points in an area of 50 by 55 km around Schiphol Airport (see previous chapter) using the STACKS+ dispersion model. The STACKS+ is a gaussian plume model that is a frequently used model for the dispersion of aircraft emissions in the Netherlands.

Calculations are based on emission data, actual flight data obtained from the FANOMOS (Flight track and Aircraft Noise Monitoring System) database maintained by the NLR-Netherlands Aerospace Centre (NLR) and meteorological data from the Schiphol Airport KNMI station. In addition to actual flight movements, NLR provides data on fuel consumption and emission factors for PM and NOx for the different phases of flight (taxiing, starting, climbing, approaching, landing).

We evaluated the applicability of the dispersion model STACKS+ to assess long-term exposure to UFP from aviation as part of (Module I) of the UFP Schiphol research program (Voogt, 2019). A detailed comparison between modelled and measured particle number concentrations (PNC) due to aircraft emissions was carried out at ten locations in the surroundings of Schiphol Airport during 6-month periods in 2017 and 2018. Since real world emission factors for PNC from aircraft are lacking, both emission estimates for PM and NO_X as a proxy and indicative emission factors for UFP derived from literature were applied (Mazaheri et al., 2009).

Half-year average predictions of the model showed a good agreement with measurements of aircraft contributions. It was concluded that the model was suitable for application in epidemiological studies among residents around Schiphol Airport. Applying the indicative emission factors for UFP from literature yielded a slightly better agreement between model and measurements (Spearman and Pearson correlation coefficients of 0.84-0.90 respectively) than applying the emissions factors for PM and NO_X as a proxy, and this indicator is used in our further studies.

The methodology includes the derivation of a scale factor allowing the model results to be adjusted to the measurements. The method to derive this scale factor has recently been refined. In the earlier analysis, expert judgement was used to estimate the contribution of aviation to the total measured UFP concentrations, assuming a constant background concentration. In the new analysis, the background concentration varies by wind direction and the contribution of road traffic is taken into account. This provides a more robust and reliable assessment of the UFP airport contribution. The scale factor based on the new methodology is lower than earlier scale factor (0.78 instead of 1.17). As a result, all estimates of UFP from aviation were adapted accordingly. As this is a constant factor, the spatial distribution remains unchanged. The conclusion regarding the suitability of the model for application in epidemiological studies is unaffected as well.

2.5.3 *Average exposures*

For the long-term studies hourly FANOMOS data for the period 2003-2019 (supplemented with data from 2019 early 2020) were obtained. Monthly averaged UFP contributions were calculated for a grid of 250 by 250 meter, covering the whole study area. The availability of monthly values throughout the whole study period allowed us to calculate average concentrations for varying exposure windows, depending on the requirements of the specific study (ranging from e.g. 3 monthly averages for pregnancy outcomes to multi-annual averages for mortality).

2.5.4 *Peak exposures*

Monthly values are based on hourly values, which were calculated but not saved for all hours and grid points as this dataset would become too large to manage. However, specific characteristics of the hourly distributions within a month could be saved and exported.

To get an indication of possible peak exposures, we calculated the number of hours per month above 100,000 #/cm^3, based on the earlier estimates (see 2.5.2). With the new scale factor, this corresponds to the number of hours above 66,667 #/cm^3. We then calculated the percentage of time that this concentration was exceeded. The advantage of this approach over, for example the calculation of specific percentiles of the monthly distribution, is that we could combine monthly frequency distributions later. In this way, we are flexible in the time windows for which we calculate indicators of peak concentrations. We included the indicator of peak exposure in sensitivity analyses.

2.5.5 *Exposure specification in the different studies*

As indicated in paragraph 2.5.3, we calculated monthly averages of UFP contributions from aviation for all addresses in the modelling area, for the period 2003-2019. This allows calculation of different exposure windows, including incorporating residential history during follow-up. For the study on mortality and medication use, we determined the address with the longest duration (further referred to as 'primary address') for each of the 5 years before baseline as well as for each year of follow-up. Next, we linked the corresponding annual average UFP contributions from aviation. For the health monitor, we did the same for the address at the time of the questionnaire (set at the first of September of the year of the survey) as well as the primary address in each of the 4 preceding years. For pregnancy outcomes, we linked monthly averaged UFP contributions at the corresponding addresses for the complete pregnancy as well as 3 months before pregnancy.

As estimates of UFP contributions from aviation are not available for addresses outside the modelling area, we set these values to zero for the monthly averages (used in study on pregnancy outcomes) and to 267 #/cm^3 for the annual averages (i.e. 2/3 of the lowest value within the modelling area).

Table 2.4 summarises the exposure specification used in the different studies.

Table 2.4 UFP Exposure specification (including residential history).

	Mortality	Medication use	Health monitor	Pregnancy outcomes
Exposure window	1, 3, 5[1] year moving averages; Use of a 'lag-year'	1, 2, 3, 5[1] year moving averages; the calendar year is included, so no lag-year	1, 3, 5[1] year moving averages; 1year = annual average of the year of the survey + annual average based on the 12 months before the survey[4]	6 exposure windows, based on monthly values (complete pregnancy, each of the 3 trimesters, 3 months before pregnancy and total period)
Exclusion after moving out of the study area	No (impute UFP exposure data outside study area)	No longer alive No longer lives in the same district Moved to an institution	NA (cross-sectional study)	No, UFP exposure of 0 used for months outside the study area (max 3 months; see table 2.1)
Incorporate residential history before inclusion[2]	Yes, based on primary address in each of the 5 years before baseline (used in calculation of the different moving averages)	Yes, based on primary address in each of the 5 years before inclusion (used in calculation of the different moving averages)	Yes, based on primary address in each of the 5 years before inclusion (used in calculation of the different moving averages)	No
Incorporate residential history during follow-up	Part of time-varying analysis; Lost to follow-up after moving to an unknown or ''unlinkable'' address; No further exclusion	Included (only time varying)	NA (cross-sectional study)	NA (see table 2.1 for exclusion criteria based on residential history)
Exposure specification (for covariate models see table 2.3)	Linear for all covariate models; Splines with 3 df for main model only	Linear for all covariate models; Splines with 3 df for main model only	Linear for all covariate models; Splines with 3 df for main model only	Linear for all covariate models; Splines with 3 df for main model only

[1] As exposure data is available from 2003 onwards, the widest available exposure window for mortality is 5 years. For medication use and the health monitor the same exposure windows are applied; [2] See table 2.1 for inclusion criteria on residential history; [4]Set at the first of September of the year of the survey; only included for self-reported health outcomes (i.e. not for medication).

2.6 Potential confounders

2.6.1 Background

We made use of existing health registries, available at CBS as microdata datasets. CBS combines data from the municipal basic registration of population data (Gemeentelijke Basis Administratie: GBA) into a longitudinal file for each individual (de Bruin 2004). These records start on January 1, 1995. Changes in demographic attributes (e.g. birth, death, address, marital status, emigration) are updated continuously by adding additional information on the nature and the date of the change.

In these files, the individual identification number of the GBA is replaced by a meaningless, but unique identification number. This identification number can be used to enrich the individual files with information from other central data sources maintained by CBS like the social statistics database which contains, among others things, data from the tax authorities and about employment status (Arts and Hoogteijling 2002) and with data from health registries.

Also, all addresses in the Netherlands have a unique identification number. It is possible to upload (environmental) data for the home address that is subsequently encrypted and made available by CBS for linkage to individuals.

CBS provides secured computational facilities to carry out the analyses (conditional on permission of the datasets).

2.6.2 Information available at personal or household level

Confounders are available at CBS from the civil (municipal) registry and other national registries. Data from the civil registry are available from 1995 through the most recent (last) year. This means that - over that period - for all 17 million residents in The Netherlands age, gender, marital status and migration background are available. Household type and number of household members are also available or derived from the information in the civil registry.

Yearly data on income and personal capital are calculated by CBS based on tax authority and educational (DUO) registries and are available for virtually all residents.

Information on the highest level of education achieved in the Netherlands is available for only part of the population. The figures on education are derived from a combination of sources by CBS: the Labor Force Survey (EBB), a survey conducted since 1996 among the population aged 15 years and older; several diploma registries (start dates varying from 1983 (universities) until 2008 (primary and special education)) and data from registered unemployed workers (Employee Insurance Agency, since 2010). Education types are classified according to the Standard Education Classification (SOI) of 2016. As such, coverage of the registry increased from about 6 million in 2004 to almost 12 million in 2019. Missing information on educational level is much more prevalent in the older population.

We included age, sex, marital status, migration background and household income in all studies. In addition, we included registry data on education in the study on pregnancy outcomes. For the PHM, self-reported education was used. See tables 2.6 and 2.7.

2.6.3 *Information available at aggregated level*

Geographical area classifications are available for all addresses varying from the very large NUTS1 area (divides the country into 4 areas), to municipality, to 6 position postal code area (contains a small number of addresses, typically one side of a street). Given the size of the study area, only municipality and smaller sized area classifications are relevant for this study. The smaller sized areas are listed in table 2.5.

Table 2.5 Geographical areas within study area and their population (2018).

Area type	# areas in 2018	Area function	Average population (range)
Municipality	31	Local administration	
District	301	Part of a municipality that is seen as homogeneously based on historical or urban planning characteristics, and that consists of a cluster of neighbourhoods.	7,200 (6-74,000)
Neighbourhood	1,251	Part of a municipality that is seen as homogeneously based on historical or urban planning characteristics.	1,730 (1-12,000)

CBS provides annual databases (since 1995) with several aggregated indicators at the municipality, district and neighbourhood level ('wijk en buurtstatistieken'). A district comprises several neighbourhoods. The number of missing values increases from municipality to neighbourhood level, since results can only be reported if based on at least 10 inhabitants. Several SES related indicators are available for multiple, but not all years. Based on an inventory of data coverage (available years) and previous studies (such as ELAPSE; Brunekreef et al, 2021) we selected the following indicators:

- Mean income per inhabitant (expressed as rank).
- Unemployment rate (# of people with income support per 1000 inhabitants aged 15-64 years; expressed as rank).
- Number of inhabitants with social assistance ('bijstand') (per 1,000 households; expressed as rank).
- Percentage of inhabitants with a non-western migration background
- Degree of urbanisation (5 categories).

In addition, we obtained area-level information on education (as %high, %median, %low) for the years 2007, 2010, 2013, 2016 and 2018, through a tailor-made assignment to CBS.

All indicators (except degree of urbanisation) were expressed as rank (percentile) in the distribution across the entire Netherlands per year to account for time trends.

We linked all indicators on neighbourhood ('buurt') level.

Every four years, a social status indicator is derived for 4 position postcodes by The Netherlands Institute for Social Research (SCP) (Knol 1998). Each postal code area receives a unique ranking for social status according to the income level, unemployment rate and education level of its inhabitants. This indicator has been used in several earlier studies by RIVM. As, with the additional data on education, information is now available for all components of the score, we decided not to include the composite score in this study.

2.6.4 *Core set of confounders*

In summary, we used a core set of confounders for the statistical analysis of all health registries:

- Age
- Gender
- Marital status
- Migration background
- Household income
- Area-level SES (selection of mean income, % non-western, high/low education, unemployment rate and social assistance; see paragraph 2.8.2).

In addition, we linked degree of urbanisation. The role of degree of urbanisation in the data-analyses is discussed in paragraph 2.8.2.1.

The operationalisation of the different variables and the order in which they are entered in the different confounder models is described in paragraph 2.8.2, tables 2.6 and 2.7.

2.7 Other air pollutants and noise

2.7.1 *Air pollution*

Annual average concentrations of PM2.5, NO_2 and Elemental Carbon (EC) was estimated following the methodology used by the Dutch government in the National Air Quality Cooperation Program (https://www.nsl-monitoring.nl). Briefly, dispersion modelling is used to estimate background concentrations at a spatial resolution of 1x1 km based on emission inventory data and meteorological parameters. Next, local contributions from road traffic are calculated, using a combination of models, with a resolution of 10x10m and are added to the large-scale concentrations. Spatial concentration maps of the Netherlands are made annually and results are intensely validated and, if applicable, recalibrated using measurement data from the National Air Quality Monitoring Network (Velders et al, 2020; Wesseling et al, 2016).

Annual average concentration maps were available for the years 2000 and 2010, and from 2015 onwards (up to 2019). Air pollution concentrations were linked to all residences in the Netherlands. We linearly imputed concentrations for 2003-2009 and for 2011-2014 based on the data for 2000 and 2010, and the data for 2010 and 2015, respectively.

For the study on pregnancy outcomes, we used the temporal variation of concentrations at measurement stations of the national air monitoring network to derive moving 3 monthly average concentrations from the annual average air pollution concentrations. We used daily average concentrations measured at 10 urban and 6 regional background stations in the study area.

2.7.2 Transport noise

Aircraft noise

Aircraft noise is an important environmental exposure in the study area. The spatial pattern of aircraft noise is different from the spatial pattern of UFP from aviation, so exposures are not highly correlated (see tables 3.6; 4.4 and 6.5).

Schiphol Airport provided annual average aircraft noise levels in an area of 55 by 71 km based on actual flight tracks for the period 2003-2019. The levels were calculated according to the national reference method. We used the indicators L_{den} (average noise level over the 24-hour period) and L_{night} (8-hour night-time exposure) on a grid of 500 by 500 meters as potential confounders.

Road traffic and railway noise

Road traffic and railway noise exposure was estimated with the RIVM Standard Model Instrumentation for Noise Assessments (STAMINA), which is a model to map environmental noise from various sources for the whole of the Netherlands (Scheurs et al., 2010). The grid size is 10 by 10 m. Input variables for the calculations were information on noise sources (for road traffic noise this includes traffic intensities, speed, composition and type of road surface), building data, and ground type.

Traffic intensities for the year 2016 were used to calculate the noise levels from motor and railways. Traffic intensities for other road types were available for the year 2011; the intensities were indexed to the year 2016 for the noise calculations. We used the estimated exposure in 2016 for the whole study period, since earlier versions of the maps were not comparable due to improvement of the input data for building height and ground type over the years. Traffic intensities may have increased on some of the larger roads (motorways, larger connecting roads, connecting roads to new neighbourhoods); the annual growth in traffic intensities for major roads is approximately 2%. This means the increment in noise exposure due to increase in flow, in general, is limited to 1 dB over a period of 10 years. This will partly be compensated by improvement of emissions of individual vehicles.

2.8 Statistical analysis

2.8.1 Introduction

We used Cox proportional hazards models in the studies on mortality and on dispensing of medication. We investigated the incidence by means of a multivariate survival analysis approach. Time-to-event was defined for each study separately, as first occurrence since the start of the study. We fit Cox proportional hazards models in the presence of a set of *a priori* selected predictors and correcting for confounding due to either individual or area-level socio-economic variables. To investigate

the assumption of proportional hazards, we used visual inspection such as plots of stratified Kaplan-Meier curves for categorical variables or the landmark approach for continuous variables, and methods based on residuals.

We used logistic regression in the studies on pregnancy outcomes and the health monitor.

Confounder adjustment is described in paragraph 2.8.2. We evaluated the shape of the exposure-response curves by using natural splines with 3 degrees of freedom and conducted several sensitivity analyses, as described in paragraph 2.10.

We conducted all statistical analyses within the secured remote access environment of CBS.

We expressed the effect estimates per 3,500 #/cm^3, which corresponds to the approximate p5-p95 increment across the different sub-studies (range 3,400 – 3,800 #/cm^3). For peak exposure this corresponded to 100 hours/month.

2.8.2 Covariate adjustment

We defined several models ***a priori*** with increasing covariate adjustment:

- Model 1: Age, sex (+ some pregnancy specific variables in the study on pregnancy outcomes)
- Model 2: Model 1 + individual covariates
- Model 2b: Model 2 + lifestyle factors (only available for the health monitor)
- Model 3: Model 2 + indicators for area-level SES.

Table 2.6 presents an overview of the specific covariates for the different sub-studies. Differences between studies are mainly caused by differences in data availability. Table 2.7 provides the operationalisation of the different indicators.

An exception/discussion point of the *a priori* selection of the covariates is the selection of the specific area-level SES indicators in models 3. This is because some of these indicators are strongly correlated (see tables 3.6; 4.4 and 6.5), and the importance of the different area-level indicators can vary across the different sub-studies. For each of the four studies, we therefore selected the most appropriate set based on exploratory analyses. We describe this in more detail in the respective chapters. Education is considered a strong indicator of SES. As individual information on education is not available in the study on mortality and medication use, the selection always included at least one indicator of education on neighbourhood level in those studies.

We used data on neighbourhood level, as this is the smallest available area. Also, correlations between the different indicators were somewhat stronger on district level compared to neighbourhood level. Missing values on neighbourhood level were imputed with the values on district level *(NB: this occurs mainly for small neighbourhoods, since CBS only reports results that are based on at least 10 inhabitants)*.

2.8.2.1 Degree of urbanisation

Degree of urbanisation is generally not included in studies on the effects of air pollution because of its (strong) positive correlation with (especially traffic-related) air pollution concentrations. For UFP from aviation, given the policy to reduce the number of people around the airport, correlation in the opposite direction may be present and low degree of urbanisation could partially be an indicator of living close to the airport. We therefore did not adjust for degree of urbanisation in our main models, but included it in our sensitivity analyses (see 2.10.2).

2.8.3 Other model specifications

2.8.3.1 Time trend in exposure and health data

In the studies on mortality and medication use, we accounted for time trends in exposure and health data by strata comprising several calendar years. In the study on pregnancy outcomes, we included the year and month of birth as categorical covariates in all models. For the public health monitor, we combined the data of the two monitors and included the year of the monitor as a categorical variable in all models.

For mortality, this also accounts for the switch from manual to automatic coding of death (IRIS) that became effective from 2013 onwards. The introduction of an automated system for coding causes of death has led to some significant changes in the registered frequency of causes of death. For example, the registered mortality rate for dementia increased with 23%; Alzheimer's disease with 30% (Harteloh, 2017). This increase is explained by an increase of selection of these diseases as the underlying cause of death under the influence of international guidelines on the one hand and change of insight about a causal link between dementia and pneumonia, respiratory or urinary tract infection on the other hand.

2.8.3.2 Addressing heterogeneity in health outcomes within the study area

Within the Netherlands, regional differences in health exist (Mackenbach, 1992), which could bias correlations between environmental exposures and health effects. In some previous studies (with data for the Netherlands as a whole), we addressed unexplained regional heterogeneity in mortality by incorporating a frailty variable for each of the provinces in the Netherlands in the regression model as a random effect (e.g. Fischer et al, 2020). In another recent national study, following the ELAPSE protocol, we included the difference between neighbourhood and regional values of the different area-level SES that were included (i.e., mean income, unemployment rate percentage, non-western immigrants and the socio-economic composite score) (Klompmaker et al, 2021). We refrained from incorporating a frailty model with provinces or other regional adjustments, since the size of the study area is limited to 2 million inhabitants and the study area is unbroken.

Within the study area heterogeneity in health outcomes could occur, for example due to differences in health care. In earlier studies with medication and hospital admission data in the Schiphol region we addressed this by including 4 digit postal code as random effect (Staatsen et al., 1998; Heisterkamp et al., 2000; Houthuijs et al., 2006). A 4 digit postal code has, on average, a similar population size as a district. As introduced in paragraph 2.2.3, we applied a Cox shared

frailty model for the medication study in which the same random effect is shared by subjects in the same district to address heterogeneity by difference in treatment practise between family doctors. For mortality, we applied the municipality at baseline as a random effect. We first fitted fixed effect covariates adjustment models including area level SES variables (model 1 – model 3) before applying the shared frailty model. For pregnancy outcomes, heterogeneity could occur because of differences in midwifery practices or hospitals (see also paragraph 4.4.3.3). However, this information was not available. We explored use of municipality (as a random effect) instead and observed no improvement of the fit for any of the primary outcomes. We therefore did not include a spatial component in the main model, but included a random effect for municipality as a sensitivity analyses. For the health monitor, data were collected by 5 different municipal health services (GGD), and this is adjusted for by including GGD as a categorical variable (fixed effect).

Table 2.6 Statistical methods and confounder models.

	Mortality	**Medication use**	**Health monitor**	**Pregnancy outcomes**
Statistical method	Cox proportional hazards	Cox proportional hazards	Logistic regression	Logistic regression
Model 1	-Age (as underlying time scale) -Sex (strata)	- Age (as underlying time scale) - 3-year time periods (strata) - Sex (stratified analysis)	- Age - Sex	- Infant sex - Parity - Gestational age[2] - Birth weight[3]
Model 2	Model 1 + - marital status - migration background - household income	Model 1 + - marital status - migration background - household income	Model 1 + - marital status - migration background - household income - education	Model 1 + - maternal age - marital status - migration background - household income - maternal education
Model 2b	Not applicable (NA)	NA	Model 2 + - Smoking; Alcohol use; - BMI; Physical activity	NA
Model 3	Model 2 +: Area-level SES	Model 2 +: Area-level SES	Model 2 +: Area-level SES	Model 2 +: Area-level SES
Adjust for time trends in exposure and health data	Strata for period (2008-2012; 2013-2016; 2017-2019)	see above	Year of the survey (categorical)	Year and month of birth as categorical covariates in all models
Spatial component	Shared frailty on the basis of municipality → model 3f	Shared frailty on the basis of district → model 3f	GGD region (fixed effect)→Model 4	Random effect for municipality (sensitivity analysis)

1 Exploratory analysis showed that strata per minimum of 3 years is optimal. Given the change in coding of mortality in 2013, the breaks between periods had to include 2012 to 2013.
2 Only for low birth weight, mortality and APGAR.
3 Only for mortality and APGAR.

Table 2.7 Operationalisation of the different confounders.

	Mortality	**Medication use**	**Health monitor**	**Pregnancy outcomes**
Age	As underlying time scale	As underlying time scale	**12 categories**: 19–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50– 54, 55–59, 60–64, 65–74, 75–84, ≥85 year	**Maternal age: 5 categories:** <20, 20-29, 30-34, 35-39, =>40 **Gestational age** (if not the outcome of interest): in weeks categorical
Sex	**Strata**	**Stratified analysis**	**Categorical**	**Categorical**
Marital status	**4 categories:** Married, living together Unmarried/never married Divorced Widowed	**4 categories:** Married, living together Unmarried/never married Divorced Widowed	**4 categories:** Married, living together Unmarried/never married Divorced Widowed	**3 categories:** Married, living together Unmarried/never married Divorced / Widowed
Migration background	**7 categories:** (Dutch; the Netherlands Antilles; Suriname; Turkey; Morocco; Other, Western; Other, non-Western)	**7 categories:** (Dutch; the Netherlands Antilles; Suriname; Turkey; Morocco; Other, Western; Other, non-Western)	**7 categories:** (Dutch; the Netherlands Antilles; Suriname; Turkey; Morocco; Other, Western; Other, non-Western)	**Maternal; 7 categories:** (Dutch; the Netherlands Antilles; Suriname; Turkey; Morocco; Other, Western; Other, non-Western)
Household income	**10 categories**: ≤p1, p1-p5, p5-p10, p10-p25, p25-p50, p50-p75, p75-p90, p90-p95, p05-p99>p99	**10 categories**: ≤p1, p1-p5, p5-p10, p10-p25, p25-p50, p50-p75, p75-p90, p90-p95, p95-p99>p99	**10 categories**: ≤p1, p1-p5, p5-p10, p10-p25, p25-p50, p50-p75, p75-p90, p90-p95, p05-p99>p99	**10 categories**: ≤p1, p1-p5, p5-p10, p10-p25, p25-p50, p50-p75, p75-p90, p90-p95, p95-p99, >p99
Education	NA	NA	**3 categories**: H/M/L (self-reported)	**3 categories**: H/M/L (registration; missing values imputed)

	Mortality	Medication use	Health monitor	Pregnancy outcomes
Other, individual			Smoking: current/former/never Alcohol: current/former/never BMI (4 categories), physical activity (4 categories; quartiles)	**Parity- 2 categories:** Primipara, multipara
Area-level SES	selection of mean income, % non-western migration background, %high education, %low education, unemployment rate and social assistance ; **All categorised in 5 categories (quintiles)**	selection of mean income, % non-western migration background, %high education, %low education, unemployment rate and social assistance ; **All categorised in 5 categories (quintiles)**	selection of mean income, % non-western migration background, %high education, %low education, unemployment rate and social assistance ; **All categorised in 5 categories (quintiles)**	selection of mean income, % non-western migration background, %high education, %low education, unemployment rate and social assistance ; **All categorised in 5 categories (quintiles)**

2.9 Selection of the main model

We based the selection of the main model on the results of the fully adjusted model (table 2.6). For the study on pregnancy outcomes, we defined exposure a priori during the full 9 month pregnancy period as the main exposure window (for all outcomes except congenital anomalies). For the other studies, we selected the most appropriate exposure window by comparing model fit for 1, 3 and 5 year moving averages of UFP as a linear term. In addition, we evaluated a 2-year moving average in the study on medication use (see 5.2.4). Next, we evaluated the shape of the exposure-response curves for the selected exposure window by using natural splines with 3 degrees of freedom.

2.10 Multi-exposure models and sensitivity analyses

We performed a number of analyses to investigate the robustness of the results, including adjustment for other air pollutants and noise (2.10.1) as well as other sensitivity analyses and stratifications (2.10.2). In the interpretation of the findings, we focus on the consistency of the findings across these analyses rather than on isolated statistical significance in a specific analysis (see 2.11).

2.10.1 Multi-exposure models

2.10.1.1 Other air pollutants

For all studies, residential concentrations of PM2.5, NO_2 and EC are available for the same exposure windows as for UFP from aviation (see paragraph 2.7.1). These air pollutants showed low correlations ($R<0.3$) with UFP from aviation in all studies (see tables 3.6; 4.4 and 6.5). Correlation between PM2.5, NO_2 and EC were high ($R>0.8$), with very strong correlations between NO_2 and EC ($R>0.9$). As EC is included in PM2.5, we also considered the difference between PM2.5 and EC (PM2.5-EC) as a potential exposure variable. Correlations between PM2.5-EC and EC were somewhat lower than correlations between PM2.5(total) and EC, but similar to correlations observed between PM2.5 and NO_2. We therefore included PM2.5, NO_2 and EC separately in two-pollutant models, and only ran a 3-pollutant model for UFP, PM2.5 and NO_2.

We entered other air pollutants as linear terms. We explored the effect of adjustment using splines, which had no noteworthy impact on the associations for mortality, associations studied in the PHM and for 2 of the 3 primary pregnancy outcomes (not explored for secondary pregnancy outcomes and medication incidence). Results for prematurity are included in chapter 4 as part of the sensitivity analyses.

2.10.1.2 Transport noise

Exposure to transport noise (aircraft, road and rail traffic) may contribute to the risk of some of the health endpoints under study for UFP and is therefore a potential confounder.

UFP from aviation was moderately correlated with aircraft noise from Schiphol ($R\sim0.3$-0.5). Noise from road traffic was moderately correlated with NO_2 and EC ($R\sim0.3$-0.4). Noise from Schiphol was moderately negatively correlated with noise from rail traffic ($R\sim-0.3$) (see tables 3.6, 4.4 and 6.5).

Transport noise is modelled separately per source; there is also background noise from other sources. As a consequence lower noise levels from a certain source may no longer be distinguishable from the background noise and the potential risk of this source might be assimilated. It is therefore conceivable that due to combined noise exposure there are thresholds for health risks of transport noise, in addition to thresholds due to a biological mechanism. To evaluate for which outcomes transport noise should be considered as covariate and at what noise level the health risk may start, we consulted the recent published Environmental Noise Guidelines for the European Region (WHO, 2018) and the underlying systematic reviews on cardiovascular and metabolic effects (van Kempen et al., 2018), adverse pregnancy outcomes (Nieuwenhuijsen et al., 2017), cognition (Clark and Paunovic, 2018a) and on mental health and well-being (Clark and Paunovic, 2018b). Between 2018 and 2020 some of these reviews were updated. Sakhvidi et al. (2018) published on diabetes. Dzhambov and Lercher (2019a, 2019b) updated studies on pregnancy outcomes and on depression. Clark et al. (2020) published an update for mental health, wellbeing, quality of life, cancer, dementia, birth reproductive outcomes and cognition. In addition, we consulted individual papers to find clues on potential thresholds.

We distinguish two groups of health outcomes that are under study for UFP from aviation:

1. Health outcomes for which it is unlikely that transport noise is a relevant covariate, so adjustment for noise is not necessary: respiratory health outcomes, lung cancer and ADHD
2. Health outcomes for which there is some evidence that the risk may start between 50 and 55 dB L_{den} for which we will apply a threshold of 53 dB L_{den} (or an equivalent threshold of 43 dB for L_{night}): cardiovascular and metabolic health outcomes, neurodegenerative outcomes, depression, self-reported general health and psychological distress, pregnancy outcomes and natural mortality (cardiovascular disease contributes to premature death)

Adjustment for noise (where applicable) was conducted for all 3 noise variables at the same time (1 model per outcome), as linear terms. Analyses were conducted with Lden as well as Lnight.

2.10.2 Summary of multi-exposure models

In summary, we will run the following multi-exposure models, with the main model adjusted for:

1. PM2.5
2. NO_2
3. EC
4. PM2.5 + NO_2
5. Road noise + rail noise + noise Schiphol (where applicable; see 2.10.1.2)
6. PM2.5 + NO_2 + road noise + rail noise + noise Schiphol

Alternatively, models 4 and 6 could include PM2.5-EC and EC (instead of PM2.5 and NO_2) or model 6 could include only one of the other air pollutants.

2.10.3 Sensitivity analyses and stratifications

Table 2.8 provides an overview of the different sensitivity analyses and stratifications.

Sensitivity analyses and stratification conducted in multiple sub-studies included:

- Sensoring or excluding subjects who moved or who lived in specific municipalities during the study. The latter included:
  - The municipality of Amsterdam, since it is reported that inhabitants of metropolitans areas in the Netherlands are less healthy than people elsewhere in the country, partly due to the over-representation of vulnerable groups with increased health problems (CBS, 2006).
  - The municipalities of Beverwijk, Heemskerk, or Velsen, as these municipalities can be influenced by heavy industrial activities in the IJmond area. Exploratory measurements showed elevated UFP concentrations in the IJmond region (Weijers and Vonk, 2020).
  - The four municipalities with the lowest UFP-aviation concentrations, *i.e.*, Purmerend, Leiden, Leiderdorp, and Oegstgeest, as preliminary analyses showed patterns of decreasing risks at the lowest UFP exposures for several outcomes across the different sub-studies.
- Analyses directed to evaluate the role of time period, in relation to among others potential higher exposure error in the earlier years. We used 1-1-2013 as time demarcation to coincide with the change in coding system for mortality
- Evaluate peak exposure to UFP from aviation by using the %hours above 66,667 #/cm^3 (instead of an annual average concentration). See 2.5.4.
- Limiting the population to subjects with a Dutch background to evaluate potential uncontrolled heterogeneity in health outcomes.
- Consideration of differences in degree of urbanisation (see 2.8.3.2)
- Stratification by age (< 65 vs. ≥ 65 years) or maternal education, to evaluate effect modification.
- Complete case analyses (for sub-studies that used multiple imputations, i.e. pregnancy outcomes and PHM).

In addition, we conducted some specific additional sensitivity analyses in the study on pregnancy outcomes:

- Exclusion of infant mortality (<1st year of age) as mortality during the first year of life might also be an indicator of other health problems.
- Stratification by spontaneous onset vs. elective Caesarean sections and labour inductions (primary outcomes only), as risk factors for indicated births are different from spontaneous (preterm) birth which might result in different associations for both groups (Goldenberg et al, 2008).
- Exclude gestational age as confounder (low birth weight), as gestational age can confound the association with low birth weight or might be a link in the causal pathway.

- Exclude children with birth defects (only for infant mortality and Apgar scores), as this might be a risk factor of infant mortality and a lower Apgar score (Linhart et al, 2000).
- Stratification for normal and low birth weight to test the hypothesis that particulate matter may have a stronger influence on vulnerable populations (only for infant mortality).

Table 2.8 Sensitivity analyses and stratifications.

	Mortality	**Medication use**	**Health monitor**	**Pregnancy outcomes**
Moving/residential history	Sensor persons when moving out of the study area during follow-up		Exclude subjects who moved in the 5 years before the survey	Exclude mothers who moved during pregnancy
Urbanisation (adjust)	Yes (5 categories)		Yes (5 categories)	Yes (5 categories)
Urbanisation (stratification)	Yes, 2 strata (1+2 and ≥3)	Yes, 2 strata (1+2 and ≥3)	Yes, 2 strata (1+2 and ≥3)	Yes, 2 strata (1+2 and ≥3)
Exclude Amsterdam	Yes, exclude persons who lived in the municipality of Amsterdam one year before baseline, and sensor when moving to Amsterdam during follow-up	Yes (municipality)	Yes (municipality)	Yes, exclude mothers who lived in the municipality of Amsterdam at the date of either conception or birth
Exclude 4 municipalities with the lowest average UFP exposure[3]	Yes	Yes	Yes	Yes
Exclude IJmond	Yes, same as for Amsterdam (3 municipalities)	Yes (3 municipalities)	Yes (3 municipalities)	Yes, same as for Amsterdam
Exclude non-Dutch	Yes	Yes	Yes	Yes
Peak exposure to UFP from aviation	Yes, include % hours above 66,667 #/cm^3 (instead of average concentration)[4]	Yes, include % hours above 66,667 #/cm^3 (instead of average concentration)[4]	Yes, include % hours above 66,667 #/cm^3 (instead of average concentration)[4]	Yes, include % hours above 66,667 #/cm^3 (instead of average concentration)[4]

	Mortality	Medication use	Health monitor	Pregnancy outcomes
Time period (also see table 2.6)	Additional analyses in a cohort with baseline 1-1-2013		Stratify by year of the survey	Stratify for period: year of birth < 2013 vs. >= 2013
Other stratifications (e.g. age, education)	Effect modification for age at baseline (< 65 vs. >= 65 years)		Effect modification for age (< 65 vs. >= 65 years) and gender	Education (3 levels)
Spatial component (see 2.8.3.2)	No (part of main model)	No (part of main model)	No (part of main model)	Random effect for municipality
Other, study specific	Baseline analyses (non-time-varying)[2]		Complete case analyses	Complete case analyses Exclude infant mortality <1y) For infant mortality: - exclude birth defects - stratify for normal and low birth weight Stratify by spontaneous onset vs. elective Caesarean section and labour inductions Exclude gestational age as confounder (if not the outcome of interest)

[1] Because of the change in the coding system for cause-specific mortality, the breaks between the time periods need to include 1-1-2013; resulting in 5 years before (divided in two 2-3 year periods) and 7 years after (divided in three 2-3 year periods).
[2] Only conducted for natural cause mortality.
[3] Preliminary analyses showed patterns of decreasing risks at the lowest UFP exposures. These patterns were observed for several outcomes across the different sub-studies. See figures appendix A2.1 for the distribution of UFP concentrations per municipality.
[4] Due to rescaling of the UFP-exposure the peak-threshold is set on 2/3 of 100,000#/$cm^{3.}$

2.11 Classification of associations and integration

We conducted a large number of analyses for multiple outcomes, including both study-specific outcomes (e.g. pregnancy outcomes) as well as similar outcomes in different sub-studies (e.g. asthma). The interpretation and integration of all findings was conducted in 2 steps.

First, we evaluated the results for all individual outcomes separately. Next, we integrated the findings per type of effect (i.e. general, respiratory, cardiovascular, metabolic, mental health, nervous system and pregnancy outcomes).

In the first step, we evaluated for each individual health outcome if the findings point towards a higher risk at higher levels of UFP from aviation. If so, we subsequently classified the overall association into 3 levels of probability, i.e. "clear'', "probable'' and "possible". For the remaining health outcomes, we distinguish between "no'' and "inverse'' association. See table 2.9.

In the classification of the findings, we focus on the consistency of the findings rather than on isolated statistical significance in a specific analysis. The shapes of the exposure-response curves are considered as part of the evaluation of consistency.

In the classification of the health outcomes, we do not distinguish between primary and secondary outcomes; this distinction is used in the interpretation per type of effect. This is described in chapter 7.

Table 2.9 Classification of the association per individual health outcome.

Classification (colour)	Criteria / description
Clear (red)	Significant positive[1] association in the main model and robust in sensitivity analyses.
Probable (orange)	Significant positive[1] association in the main model but not robust in sensitivity analyses. OR Not significant in the main model but generally elevated[1] and at least borderline ($p<0.1$) significant in some of the sensitivity analyses (excluding models prior to the main model).
Possible (yellow)	Generally elevated[1], but classification as "probable'' rejected on either the criteria of (borderline) statistical significance or the shape of the exposure-response curve.
No (blue)	Effect estimates are close to unity and there is no consistent pattern of an association in either direction.
Inverse (grey)	Consistent significant association in the opposite direction (i.e. lower risk at higher levels of UFP).

[1] In the direction of a higher risk at higher levels of UFP.

2.12 Evaluation of potential residual confounding due to incomplete adjustment for lifestyle factors

The PHM includes information on lifestyle factors (e.g. smoking, alcohol use, BMI and physical activity), which is not available in the other registries. We therefore used the PHM to gain insight into potential

residual confounding by incomplete adjustment for these factors in the other sub-studies. Specifically, we used data from the PHM to:

- Evaluate the effect of adjustment for smoking, alcohol use, BMI and physical activity on the associations between UFP from aviation in the analyses of the PHM, including the (self-reported) health endpoints within the PHM as well as *prevalence* of medication use for medication groups included in the study on *incidence* of these medication groups.
- Evaluate the effect of adjustment for smoking, alcohol use, BMI and physical activity on associations between UFP from aviation and natural cause mortality in the *PHM 2012*. We did not conduct this analysis in the PHM 2016 as only 3 years of follow-up is available (2,478 deaths; 4,9%). In addition, no information is available on the number of cigarettes smoked by current smokers in the PHM 2016.
- Indirectly adjust for smoking status and BMI of associations with mortality, using the indirect adjustment technique as developed by Shin et al (2014), and applied in ELAPSE (Stafoggia et al, 2022). The method uses information contained within the health monitor regarding the multivariate relationships between the missing lifestyle covariates (dependent variable) and UFP from aviation, adjusting for observed covariates in the main model of the mortality study. We drew a randomly stratified sample of the PHM 2012 and 2016 with information on smoking status (current, former, never smokers) and BMI (four WHO categories) with distribution of covariates (age, sex, marital status, migration background, household income) similar to the study population in the mortality study. The combined sample included 3,333 observations. We obtained effect estimates for associations of smoking status and BMI with non-accidental mortality from a European cohort of more than 300,00 adults in the ELAPSE study (Brunekreef et al, 2021).
- Evaluate the relation between exposure to UFP from aviation and lifestyle factors, by specifying linear models with the exposure as the dependent variable and lifestyle covariates (e.g. smoking status, BMI) and all covariates included in the main model as independent variables. This provides insight into potential differences in UFP exposure for, among others, current smokers compared to never smokers and obese people compared to normal weight people. We conducted these analyses within the stratified sample used for the indirect adjustment for *mortality* (n=3,333). In addition, we created two subsets that could provide insight into potential bias in the study on *pregnancy outcomes*:
  1. all women that were pregnant on the date of the survey (irrespective of the duration of the pregnancy at that time) (n=550) and
  2. a stratified sample of all women that participated in the health monitor, with the same distribution in age, education and migration background as the mothers in the study on pregnancy outcomes (n=3,064).

  The first subset did not include sufficient subjects to allow further stratified sampling on covariates. The second subset included

mainly non-pregnant women and was used to confirm findings in the first subset in a larger population.

2.13 Appendix

The figure below shows the distribution of UFP exposure per municipality, ranked from lowest (left) to highest (right) (lower). The 10 'new' municipalities (see paragraph 2.4) are indicated in grey. Four municipalities were clearly identified as having the lowest UFP exposure. These are located in the Northeastern corner (Purmerend) and Southwestern corner (Leiden, Leiderdorp and Oegstgeest) of the study area.

The figure shows the 12 year average exposure (2007-2018) of all 2 million residents in the area on 1-1-2008. Distributions of exposures during pregnancy and for participants of the health monitor identified the same 4 municipalities as those with the lowest exposure (with some variation in the exact rank).

The mean 12 year average exposure varied from 780 #/cm^3 in Purmerend to 4,200 #/cm^3 in Haarlemmermeer.

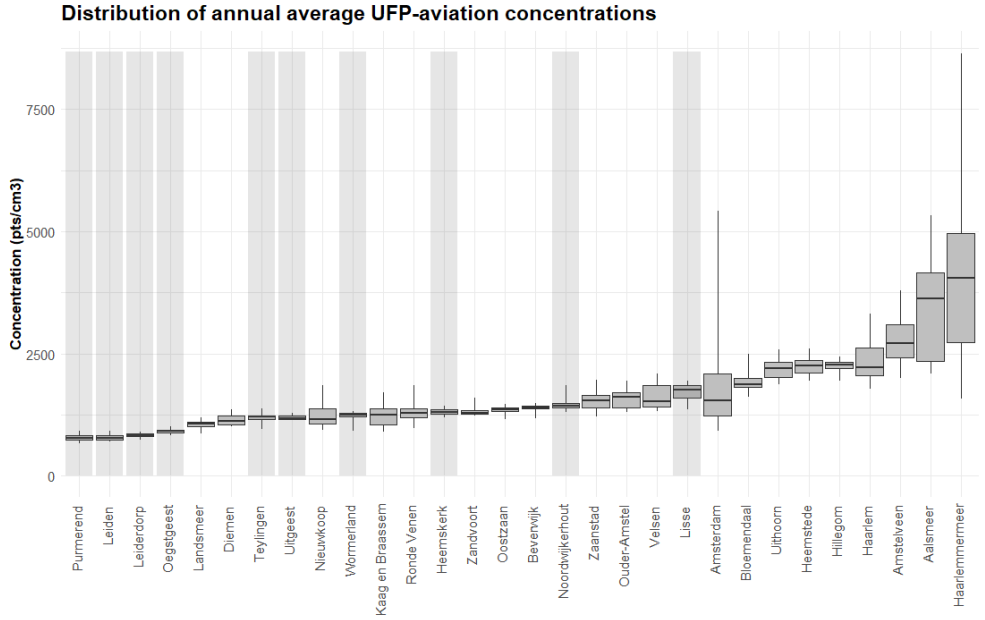


Figure A.2.1 Distribution of the 12 year average exposure to UFP from aviation per municipality (2007-2018; Haarlemmerliede and Spaarnwoude combined with Haarlemmermeer). The box shows the 25th percentile, median and 75th percentile; whiskers extent to the 1st and 99th percentile.

3 Mortality

3.1 Objectives

The objective of this study is to investigate the associations between long-term residential exposure to UFP from aviation and mortality in adult residents of the study area.

3.2 Methods

3.2.1 Study design

We studied the association between long-term exposure to UFP from aviation and natural and cause-specific mortality in the study area consisting of 31 municipalities fully included in the 50*56 km modelling area around Schiphol Airport on 1-1-2008 (Figure 2.1). This date was chosen to allow sufficient time in the health effects analysis between the start of the study and the last expansion of Schiphol Airport in 2003, which influenced the spatial distribution of exposure to UFP from aviation.

3.2.2 Study population

We created an administrative cohort that includes all the study area residents aged ≥ 30 years on 1-1-2008. We used data from several databases at CBS to compile the cohort, including the longitudinal mortality registry for follow-up, individual covariates (such as sex, marital status, or standardised household income), and neighbourhood-level socio-economic status covariates (such as mean income, or education). We excluded subjects with missing data on residential history or exposure in the five years before baseline or subjects who had a primary address outside the study area in 2007. Chapter 2.4 describes the study area extensively. The follow-up period of the cohort was from 1-1-2008 to 31-12-2019 (*i.e.*, 12 years).

3.2.3 Health outcomes

Chapter 2.3 describes the rationale behind the selection of health outcomes . In this study, we defined mortality based on the underlying cause of death recorded on death certificates in mortality registry as International Classification of Disease (ICD)-10 codes. As primary endpoints, we analysed mortality from natural causes, cardiovascular disease, respiratory disease, lung cancer, and neurodegenerative disease. Neurodegenerative disease mortality included dementia, Parkinson's disease, Alzheimer's disease and multiple sclerosis. As secondary endpoints, we included more specific causes of death, such as ischemic heart disease, myocardial infarction, arrhythmia, cerebrovascular disease, stroke, diabetes, and COPD. We also analysed dementia, Alzheimer's disease, and Parkinson's disease separately, as these were the most prevalent specific causes of death within the neurodegenerative disease endpoint. Table 3.1 presents the ICD-10 codes of the primary and secondary endpoints.

Table 3.1 Overview of the included mortality endpoints and the associated ICD-10 codes.

Primary health endpoints

- Natural (A00-R99)
- Cardiovascular disease (I10-I70)
- Respiratory disease (J00-J99)
- Lung cancer (C34)
- Neurodegenerative disease (F00-F03; G20-G22; G30; G35)

Secondary health endpoints

- Ischemic heart disease (I20-I25)
- Myocardial infarction (I21-I22)
- Arrhythmia (I46-I49)
- Cerebrovascular disease (I60-I69)
- Stroke (I60-I64)
- Diabetes (E10-E14)
- COPD (J40-J44, J47)
- Dementia (F00-F03)
- Alzheimer's disease (G30)
- Parkinson's disease (G20-G22)

3.2.4 Assessment of exposure to UFP from aviation

Chapter 2.5 describes the modelling of exposure to UFP from aviation in detail. For this study, we calculated annual averaged UFP contributions for the period 2003-2019 for a grid of 250*250 meter, covering the whole study area. We also calculated average concentrations for 3- and 5-year multi-annual averages, in order to investigate whether these may reflect exposure better than 1-year averages. Additionally to the UFP concentrations, in order to get an indication of possible peak exposures, we also calculated the annual average of hours per month with UFP concentrations above 66,667 #/cm^3 (see 2.5.4).

When assigning the annual exposure, we determined the address with the longest duration in a specific year. Next, we linked the corresponding annual average concentration of UFP from aviation. As estimates of UFP contributions from aviation were not available for addresses outside the modelling area, we set these values to 267 for the annual averages (*i.e.*, 2/3 of the lowest value within the modelling area).

3.2.5 Potential confounders

Chapter 2.6 provides more detailed information on potential confounders.

3.2.5.1 *Information available at personal or household level*

Individual confounders are available at CBS from the civil (municipal) registry and other national registries. In the current study, we included age, gender, marital status, migration background, and household income. There was some missing information on income data, which we interpolated. If more than 4 out of 12 follow-up years were missing, these subjects were excluded.

3.2.5.2 *Information available at area level*

We selected the following indicators:

- Mean income per inhabitant.
- Number of people with unemployment benefit (per 1,000 inhabitants aged 15-64 years).
- Number of inhabitants with social assistance (per 1,000 households).
- Percentage of inhabitants with a non-western migration background.
- Education (3 categories expressed in percentage: high, mid, low).

We obtained the information on education for the years 2007, 2010, 2013, 2016, and 2018, through a tailor-made assignment to CBS. All indicators were linked on neighbourhood (*buurt*) level, which is the smallest available area, and were expressed as rank (percentile) in the distribution across the entire Netherlands per year to account for time trends.

In addition, we linked degree of urbanisation (5 categories) on the neighbourhood level. Degree of urbanisation is generally not included in studies on the effects of air pollution because of its (strong) positive correlation with (especially traffic-related) air pollution concentrations. For UFP from aviation, given the policy to reduce the number of people in the vicinity of the airport, correlation in the opposite direction may be present and low degree of urbanisation could partially be an indicator of living close to the airport. To test this assumption, we adjusted for degree of urbanisation in our sensitivity analyses.

3.2.5.3 Other air pollutants and transportation noise

3.2.5.3.1 *Air pollution*

We included annual average concentrations of PM2.5, NO_2, and EC as co-pollutants in our study. Chapter 2.7 provides more information on the co-pollutants modelling methodology .

3.2.5.3.2 *Transport noise*

We included annual average aviation noise levels from Schiphol, as well as road-traffic and railway noise exposures.

Chapter 2.7 provides more information on noise exposure assessment.

3.2.6 Statistical analyses

We analysed the associations between exposure to UFP from aviation and natural and cause-specific mortality using Cox proportional hazards models stratified by sex and calendar period with age as underlying timescale and random term for municipality at baseline. We focused on a single occurrence of a single type of event, examining time-to-event in relation to an *a priori* selected set of explanatory variables. We used time-varying exposure analyses to account for residential history and time trends in exposure, area-level SES covariates, and mortality during follow-up. Censoring occurred at the time of the event of interest death from other causes, emigration, loss to follow-up for other reasons, or the end of follow-up, whichever came first. We investigated the assumptions underlying the Cox model by studying plots of the non-

parametric Kaplan-Meier estimator and plots of the logarithm of the cumulative hazard against log-time.

By stratifying for calendar period, we accounted for time trends in exposure, area-level SES, and health data. The latter is also important due to a switch from manual to automatic coding causes of death that became effective from 2013 onwards. Therefore, we chose three calendar periods: 5 years (2008-2012), 4 years (2013-2016) and 3 years (2017-2019). The introduction of the automated coding system has led to some significant changes in the frequency of causes of death. For example, the mortality rate for dementia increased with 23% and for Alzheimer's disease with 30% (Harteloh, 2017). This increase is explained by an increase of selection of these diseases as the underlying cause of death under the influence of international guidelines on the one hand and change of insight into a causal link dementia and pneumonia, respiratory or urinary tract infection on the other hand.

Analyses were performed in R in a secure remote-access computational environment of CBS.

3.2.6.1 Main analyses

We specified three confounder models *a priori*, with an increasing level of adjustment for individual and area-level covariates. Model 1 included: age (as the timescale), sex (strata), and calendar period (strata). Model 2 further included individual covariates: marital status, migration background, and household income. Model 3 further expanded model 2 with neighbourhood-level SES.

An exception to the *a priori* selection of the covariates was the selection of the specific area-level SES indicators. The reason for this is that some of these indicators were highly correlated (Table 3.6). We therefore performed an exploratory analysis in which we added step-by-step area-level SES covariates until the model fit (described by Akaike Information Criterion, AIC) did not improve anymore, paying attention to the direction of the area-level covariates' associations. Since education is considered a strong indicator for SES and individual information on education was not available, the selection always included at least one indicator of education on neighbourhood level (either high or low education percentage). Based on the results of the exploratory analysis, we included area-level income, percentage of inhabitants with non-western migration background, and percentage of inhabitants with low education in model 3.

We incorporated a frailty model with municipality at the baseline address to address spatial heterogeneity within the study area in all models.

Selection of the main model was based on the results of model 3. The most appropriate exposure window was selected by comparing model fit (AIC) for 1 year and 3- and 5-year moving averages of UFP from aviation. Next, we assessed the shape of the concentration-response relationship between UFP from aviation and mortality using natural cubic splines with three degrees of freedom. Based on this examination, we chose model 3 with 1-year UFP-aviation average in the preceding year entered as a linear term as the main confounder model.

3.2.6.2 Multi-exposure models

3.2.6.2.1 *Other air pollutants*

For all studies, residential concentrations of PM2.5, NO_2, and EC were available for the same exposure windows as for UFP from aviation. As EC is included in PM2.5, we also considered the difference between PM2.5 and EC (*i.e.*, PM2.5-EC) as a potential exposure variable. Due to correlations between the air pollutants (Table 3.6), we included PM2.5, NO_2, and EC separately in two-pollutant models.

3.2.6.2.2 *Transport noise*

Exposure to transport noise (aviation, road, and rail traffic) may contribute to the risk of some of the health endpoints under study for UFP and was therefore included as a potential confounder in multi-pollutant models. In four-pollutant models, we adjusted UFP from aviation for all available noise variables, whereas in five-pollutant models, we expanded four-pollutant models with PM2.5, NO_2, or EC.

At lower levels, transport noise may no longer be distinguishable from the background noise and the potential risk of this source might be assimilated. To account for this possibility, we included noise level thresholds at which the health risks may start.

Chapter 2.10 presents the extensive rationale behind the choice of thresholds. Briefly, for the health outcomes for which there is some evidence that noise is a relevant covariate (*i.e.*, cardiovascular diseases, diabetes, natural mortality, as cardiovascular disease contributes to premature death, and neurodegenerative diseases), we assigned a value of 53 dB Lden to all noise levels < 53 dB Lden.

3.2.6.3 (Other) sensitivity analyses and stratifications

We performed a number of sensitivity analyses to investigate the effect of (see 2.10.2 for rationale):

- peak UFP exposure, *i.e.*, hours above 66,667 #/cm^3 instead of average concentration.
- using exposure of the baseline year 2008, instead of time-varying exposure.
- changing residence, specifically living outside the study area 1 year before baseline, or moving outside the study area during follow up.
- living in the municipality of Amsterdam 1 year before baseline, or moving to Amsterdam during follow up.
- living in the municipalities of Beverwijk, Heemskerk, or Velsen 1 year before baseline, or moving there during follow up, as these municipalities can be influenced by heavy industrial activities in the IJmond area.
- living in the four municipalities with the lowest UFP-aviation concentrations, *i.e.*, Purmerend, Leiden, Leiderdorp, and Oegstgeest, 1 year before baseline, or moving there during follow up.
- limiting the population to subjects with a Dutch background.
- effect modification by age at baseline (< 65 vs. ≥ 65 years).
- differences in degree of urbanisation by stratifying for high (categories 1-2) vs. low urban (categories 3-5) urbanisation.

3.3 Results

3.3.1 Study population

Our cohort consisted of 1,259,578 subjects aged ≥ 30 years who contributed 13,603,661 person-years at risk of follow-up. In the time-varying exposure dataset our subjects contributed 13,726,158 observations. Table 3.2 presents population characteristics. Compared to the population ≥ 30 on 1-1-2008 in the entire Netherlands (Klompmaker et al, 2021), the study population included less married subjects (54.5% vs 63.0%), less subjects of Dutch origin (74.5% vs. 82.7%) and more subjects with a mean household income above the 90th percentile (16.5% vs. 12.5%).

3.3.2 Health outcomes

We observed 185,348 non-accidental deaths (Table 3.3), of which 47,952 cardiovascular disease deaths, 17,460 respiratory disease deaths, 13,802 lung cancer deaths and 19,472 neurodegenerative disease deaths. Of all cardiovascular deaths, ~26% died from ischemic heart disease and ~26% died from cerebrovascular disease. Of all respiratory deaths, ~50% died because of COPD, and of all neurodegenerative deaths ~61% were dementia deaths.

Table 3.2 Population characteristics at baseline (N=1,259,578).

Covariate	Category	N (%) or mean (SD)	
Age		53.0	(15.1)
Sex	Male	608,547	(48.3)
	Female	651,031	(51.7)
Marital Status	Married	686,045	(54.5)
	Widowed	97,070	(7.7)
	Divorced	157,124	(12.5)
	Single	319,339	(25.4)
Region of origin	The Netherlands	939,005	(74.5)
	Morocco	34,970	(2.8)
	Turkey	30,336	(2.4)
	Suriname	50,174	(4.0)
	Antilles Netherlands	9,248	(0.7)
	Other non-western	52,990	(4.2)
	Western	142,855	(11.3)
Standardised household income*	<1%	10,109	(0.8)
	1-5%	22,585	(1.8)
	5-10%	46,136	(3.7)
	10-25%	162,504	(12.9)
	25-50%	268,902	(21.3)
	50-75%	316,794	(25.2)
	75-90%	224,538	(17.8)
	90-95%	85,599	(6.8)
	95-99%	78,308	(6.2)
	>99%	44,103	(3.5)

* Percentile of the distribution in the whole Netherlands.

Table 3.3 Number of cases of selected specific causes of death in the cohort.

Description	n	%
Natural mortality (non-accidental)	**185,348**	**100**
Respiratory disease	**17,460**	**9.4**
COPD	8,789	4.7
Cardiovascular disease	**47,952**	**25.9**
Ischemic heart diseases	12,603	6.8
Myocardial infarction	7,775	4.2
Arrhythmia	5,330	2.9
Cerebrovascular diseases	12,403	6.7
Stroke	10,508	5.7
Diabetes	4,020	2.2
Neurodegenerative disease	**19,472**	**10.5**
Dementia	11,975	6.5
Parkinson's disease	2,198	1.2
Alzheimer's disease	4,941	2.7
Multiple sclerosis	358	0.2
Lung cancer	**13,802**	**7.4**

N=1,259,578. Primary endpoints in bold.

3.3.3 Exposure

3.3.3.1 Distribution of UFP from aviation, other air pollutants and noise

Average residential exposure to UFP from aviation was about 1800 #/cm^3 (Table 3.4). Variation was larger for UFP from aviation compared to the other air pollutants or noise (relative SD = 0.65 compared to

0.11-0.27). The proposed cut-off value of 53 dB for noise (Lden) is exceeded in < 5% of the observations for aviation noise from Schiphol and noise from rail traffic (P95 < 53 dB) and about 50% of the observations for noise from road traffic.

Table 3.5 presents the distribution of UFP from aviation for the different categories of degree of urbanisation. We did not observe any clear pattern of increasing or decreasing concentrations with degree of urbanisation.

3.3.3.2 Correlation between UFP from aviation, other air pollutants, noise and neighbourhood SES

Table 3.6 presents Spearman correlation coefficients between UFP from aviation, other air pollutants, noise, and indicators for neighbourhood SES. We found weak correlations of UFP from aviation to most of the other exposure and indicators of area-level SES, with the strongest correlation to aviation noise from Schiphol (R = 0.46); all other correlations were < 0.18. Noise from road traffic was moderately correlated NO_2 and EC (R = 0.31-0.35), whereas aviation noise from Schiphol was moderately negatively correlated with noise from rail traffic (R < -0.31). Annual average residential concentrations of the co-pollutants (PM2.5, NO_2, and EC) were

strongly correlated (R > 0.82). For the different indicators of area-level SES included in the main model, we observed strong negative correlation between mean income and percentage low education (R = -0.79), and moderate correlations between the percentage of inhabitants with non-western migration background with mean income (R = -0.50), and the percentage of inhabitants with low education (R = 0.27).

We present Spearman correlation coefficients between the different exposure metrics and exposure windows for UFP from aviation in Table 3.7. All exposure metrics were highly correlated (R > 0.8).

Table 3.4 Distribution of annual average concentrations of UFP from aviation, other air pollutants, and noise.

	Mean	SD	P1	P5	P10	P25	P50	P75	P90	P95	P99
UFP-aviation	1,831	1,188	267	683	809	1,099	1,503	2,181	3,293	4,294	6,307
PM2.5	14.30	2.40	10.20	10.80	11.20	12.30	14.20	16.20	17.50	18.30	20.00
NO2	26.00	5.00	15.30	18.10	19.70	22.60	25.80	29.30	32.50	34.50	37.60
EC	1.10	0.30	0.60	0.70	0.70	0.80	1.00	1.20	1.50	1.60	1.90
PM25-EC	13.30	2.10	9.50	10.00	10.40	11.50	13.20	14.90	16.10	16.70	18.10
Aviation (Schiphol) noise	45.90	5.00	20.00	41.00	41.80	43.50	46.00	48.20	51.00	52.90	57.10
Road traffic noise	53.30	6.40	40.50	43.80	45.60	48.70	52.80	57.60	62.10	64.70	69.00
Rail traffic noise	35.40	9.00	24.00	24.00	24.00	28.40	34.50	41.10	48.10	52.00	58.90

N=13,726,158. UFP in #/cm^3, other air pollutants in µg/m^3, noise (Lden) in dB.

Table 3.5 Distribution of UFP from aviation stratified by degree of urbanisation.

Degree of urbanisation	n	Mean	SD	P1	P5	P10	P25	P50	P75	P90	P95	P99
1 > 2,500 addr./km2	6,080,883	1,808	984	267	716	847	1,173	1,574	2,175	3,026	3,837	5,395
2 1,500-2,500 addr./km2	3,947,986	1,836	1,318	267	657	753	994	1,405	2,205	3,684	4,710	6,651
3 1,000-1,500 addr./km2	1,820,278	1,993	1,445	267	711	881	1,150	1,515	2,392	3,667	4,688	8,071
4 500-1,000 addr./km2	1,142,424	1,838	1,244	267	267	869	1,082	1,462	2,094	3,629	4,543	6,135
5 < 500 addr./km2	734,587	1,582	1,152	267	267	621	987	1,335	1,863	2,743	3,537	5,958

N=13,726,158. UFP in #/cm3.

Table 3.6 Spearman's correlations between UFP from aviation, other air pollutants, noise, and indicators for neighbourhood SES.

	Other air pollutants				Noise			Neighbourhood SES					
	PM2.5	**NO_2**	**EC**	**PM2.5 - EC**	**Aviation**	**Road traffic**	**Rail traffic**	**Income**	**High edu.**	**Low edu.**	**Unempl.**	**Social assist.**	**% non-western**
UFP-aviation	-0.06	0.08	0.03	-0.07	0.46	0.08	-0.18	0.11	0.04	-0.02	0.00	-0.03	0.08
PM2.5	1.00	0.82	0.88	1.00	-0.09	0.16	0.16	0.05	0.21	-0.14	-0.03	0.19	0.23
NO_2		1.00	0.95	0.79	-0.07	0.35	0.31	0.06	0.38	-0.24	0.10	0.35	0.44
EC			1.00	0.85	-0.10	0.31	0.30	0.06	0.35	-0.23	0.07	0.31	0.40
PM2.5-EC				1.00	-0.09	0.14	0.14	0.04	0.18	-0.13	-0.04	0.17	0.20
Aviation (Schiphol) noise					1.00	-0.05	-0.31	-0.04	-0.23	0.17	-0.13	-0.08	0.02
Road traffic noise						1.00	0.17	0.03	0.18	-0.11	0.09	0.16	0.16
Rail traffic noise							1.00	0.07	0.34	-0.25	0.16	0.20	0.18
Mean income								1.00	0.71	-0.79	-0.31	-0.61	-0.50
% High education									1.00	-0.88	-0.12	-0.21	-0.07
% Low education										1.00	0.21	0.41	0.27
Unemployment rate											1.00	0.56	0.47
Social assistance												1.00	0.81

N=13,726,158.

Table 3.7 Spearman's correlation between different UFP exposure metrics.

UFP-aviation annual average	Concentration (#/cm^3)			Peak (hours/month)		
	1 year	3 year	5 year	1 year	3 year	5 year
1 year	1.00	0.95	0.93	0.87	0.83	0.81
3 year*		1.00	0.99	0.85	0.88	0.86
5 year*			1.00	0.84	0.88	0.88
Peak, 1 year				1.00	0.96	0.94
Peak, 3 year					1.00	0.99

* 3 and 5 year values incorporated changes in address. N=13,726,158.

3.3.4 Associations between UFP from aviation and primary outcomes

3.3.4.1 Main model

In general, we observed no associations between UFP from aviation and natural and cause-specific mortality (Table 3.8). The associations for all primary outcomes were slightly negative, with the associations for neurodegenerative disease mortality being statistically significant, driven by dementia and Parkinson's disease mortality. Adjustment for individual and neighbourhood SES through models 1-3 generally diminished but did not fully explain the observed associations. Adjustment for individual SES in model 2 generally turned the direction of the associations into positive, which was again reversed by adjustment for neighbourhood SES. Using 3- and 5-years moving averages instead of 1-year average made the associations with the primary outcomes somewhat more negative (Figure 3.1).

Figures 3.2 shows the shape of concentration-response functions for UFP from aviation and primary mortality outcomes. We generally saw the same picture in the linear analysis, with the associations' confidence interval including unity at nearly every UFP concentration, meaning a lack of a statistically significant association. For neurodegenerative disease mortality, the pattern was difficult to interpret as we observed a decreasing trend at the lowest exposures. The shape of the curve could not be interpreted at high UFP concentrations as indicated by wide confidence intervals, related to sparsity of data (Figure A.3.1).

3.3.4.2 Sensitivity analyses and stratifications

In two-pollutant models, the association between UFP from aviation and primary mortality outcomes remained unchanged after adjustment for PM2.5, NO_2, EC, or noise (Figure 3.3). Only for neurodegenerative disease, the previously observed negative association with UFP was no longer significant after adjusting for NO_2 (with and without noise) and EC (together with noise).

When we used baseline 2008 air pollution exposure instead of time-varying exposure, the associations between UFP from aviation and natural mortality became more negative and statistically significant (Figure 3.4). Because of the change in disease coding in 2013, we could not investigate the associations with baseline exposure for cause-specific mortality. To address that, we created an additional cohort with 2013 as baseline. These results are presented in the Appendix.

We found indications of effect modification with respect to age, where the negative associations observed in full population changed direction in the group < 65 years for almost all primary mortalities (Figure 3.4). For lung cancer mortality, we observed the opposite, with the risk for the group ≥ 65 years becoming slightly positively associated with UFP-aviation exposure.

We also observed an indication of effect modification by the degree of urbanisation, with the associations in the low-urban areas drawn towards null for natural mortality, or changing the association direction to slightly positive for cardiovascular and lung cancer mortality (Figure 3.4).

When we investigated the association between the percentage of time with peak UFP exposure and mortality (instead of average UFP exposure), the associations for natural and respiratory mortality became positive, and the association for cardiovascular mortality became null (all non-significant; Figure 3.4).

In the sensitivity analyses where we excluded subjects who lived in certain areas a year before baseline or those who moved there during follow-up (*i.e.*, Amsterdam, IJmond area, four municipalities with lowest UFP exposure) or the subjects who moved out of the study area during the follow up, we found different results across primary endpoints (Figure 3.4). For natural and cardiovascular mortality, excluding subjects living in / moving to Amsterdam resulted essentially in nullifying the negative connections observed in the full population, whereas the association for neurodegenerative mortality became more negative. For respiratory disease mortality, excluding subjects living in/moving to the four municipalities with the lowest concentrations, reversed the direction of the negative association.

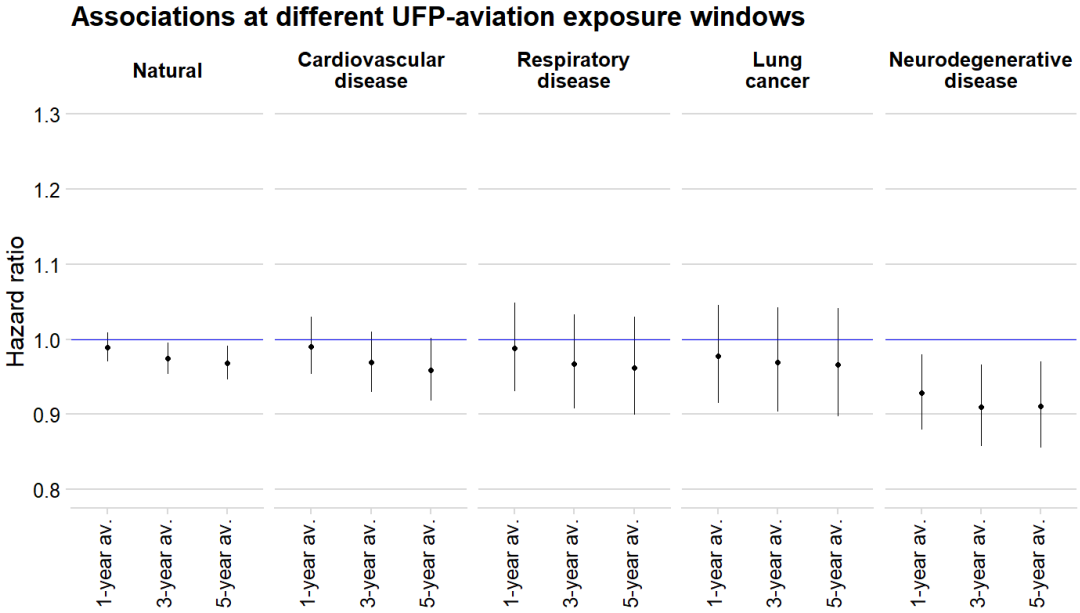


Figure 3.1 Associations between UFP from aviation and primary outcomes at different exposure windows. N=13,726,158. Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for 3,500 #/cm^3 increase in UFP.

Table 3.8 Risk of death associated with exposure to UFP from aviation.

Mortality	HR (95% CI)		
	Model 1	Model 2	Model 3
Natural	0.893 (0.875, 0.910)	1.015 (0.996, 1.035)	0.990 (0.971, 1.009)
Cardiovascular disease	0.893 (0.860, 0.928)	1.014 (0.976, 1.053)	0.991 (0.954, 1.029)
Respiratory disease	0.879 (0.824, 0.935)	1.020 (0.962, 1.082)	0.988 (0.931, 1.048)
Lung cancer	0.933 (0.870, 1.000)	1.007 (0.942, 1.077)	0.978 (0.915, 1.045)
Neurodegenerative disease	0.783 (0.741, 0.826)	0.959 (0.911, 1.011)	0.929 (0.880, 0.980)
Ischemic heart disease	0.938 (0.872, 1.008)	1.038 (0.967, 1.113)	0.995 (0.928, 1.065)
Myocardial infarction	0.947 (0.866, 1.036)	1.044 (0.956, 1.140)	0.986 (0.905, 1.075)
Arrythmia	0.975 (0.883, 1.076)	1.073 (0.971, 1.185)	1.084 (0.980, 1.198)
Stroke	0.902 (0.841, 0.966)	0.998 (0.931, 1.070)	0.985 (0.916, 1.060)
Cerebrovascular disease	0.910 (0.851, 0.972)	1.027 (0.962, 1.096)	1.012 (0.944, 1.082)
COPD	0.902 (0.826, 0.983)	1.058 (0.973, 1.152)	1.021 (0.938, 1.111)
Diabetes	0.915 (0.807, 1.038)	1.117 (0.993, 1.258)	1.032 (0.919, 1.158)
Dementia	0.708 (0.656, 0.766)	0.906 (0.844, 0.972)	0.890 (0.829, 0.956)
Alzheimer's disease	0.882 (0.791, 0.983)	1.097 (0.991, 1.214)	1.043 (0.938, 1.160)
Parkinson's disease	0.767 (0.664, 0.887)	0.886 (0.768, 1.022)	0.857 (0.739, 0.992)

N=13,726,158. Primary endpoints in bold. Hazard ratios (95% confidence intervals) presented for 3,500 #/cm^3 increase in UFP. Model 1 included age (as the timescale), sex (strata), calendar period (strata), and municipality at baseline (random); model 2 further adjusted for marital status, migration background, and household income; model 3 added neighbourhood-level income, percentage of inhabitants with non-western migration background, and percentage of inhabitants with low education.

3.3.4.3 Missing lifestyle information

The cohorts based on administrative data often lack information on individual lifestyle-related risk factors. A study in the Netherlands showed that even weak associations between long-term air pollution exposure and these factors, *e.g.*, smoking or BMI, may substantially affect air pollution mortality risk estimates (Strak, 2017a).

3.3.4.3.1 *Associations between UFP-aviation and lifestyle variables*

From the same study area, we drew randomly stratified samples of participants in the PHM 2012 and 2016 (chapter 6) with information on smoking status (current, former, never smokers) and BMI (four WHO categories) with distribution of covariates (age, sex, marital status, migration background, household income) similar to our study population. The combined sample included 3,333 observations. We then estimated the association between smoking status and BMI (as dependent variables) and UFP from aviation (as independent variable) in PHM using linear regression. The results showed that being current smoker was associated with 56 #/cm^3 lower UFP exposure than experienced by never smokers (Table 3.9), whereas being overweight or obese was associated with 115 #/cm^3 and 36 #/cm^3 higher UFP exposure than in subjects with normal-range BMI. All differences were

non-significant, with the exception of the difference between overweight and normal-weight subjects.

Table 3.9 Associations between UFP-aviation and lifestyle variables.

Variable	Level	Estimate (SE)
Smoking	Current	-56 (59)
	Former	33 (51)
BMI	Underweight	-22 (237)
	Overweight	115 (49)
	Obese	36 (67)

N = 3,333. Reference levels: never smokers and normal-weight BMI (18.5-24.9 kg/m^2). Model: UFP-aviation = smoking + BMI + age + sex + marital status + migration background + household income + neighbourhood-level income + percentage of inhabitants with non-western migration background + percentage of inhabitants with low education.

3.3.4.3.2 Indirect adjustment for missing lifestyle information

We used the indirect adjustment technique as developed by Shin and colleagues (2014), and recently applied in ELAPSE (Stafoggia, 2022). We indirectly adjusted the natural mortality risk estimate by multiplying the associations between UFP-aviation exposure and smoking & BMI observed in the stratified PHM sample (see 3.3.4.3.1) with the estimates of associations between smoking status & BMI and mortality derived from literature. The resulting value was then added to the (unadjusted) risk estimates from our main analysis. After indirect adjustment, natural mortality HR changed direction and became slightly positive, without reaching statistical significance (Table 3.10).

Table 3.10 Effect of indirect adjustment for missing lifestyle factors on risk of natural mortality.

Mortality	Type	HR (95% CI)
Natural	Unadjusted	0.990 (0.971, 1.009)
	Adjusted	1.005 (0.986, 1.025)

Hazard ratios (95% confidence intervals) presented for 3,500 #/cm^3 increase in UFP-aviation. Model 3 included age (as the timescale), sex (strata), calendar period (strata), municipality at baseline (random), marital status, migration background, household income, neighbourhood-level income, percentage of inhabitants with non-western migration background, and percentage of inhabitants with low education.

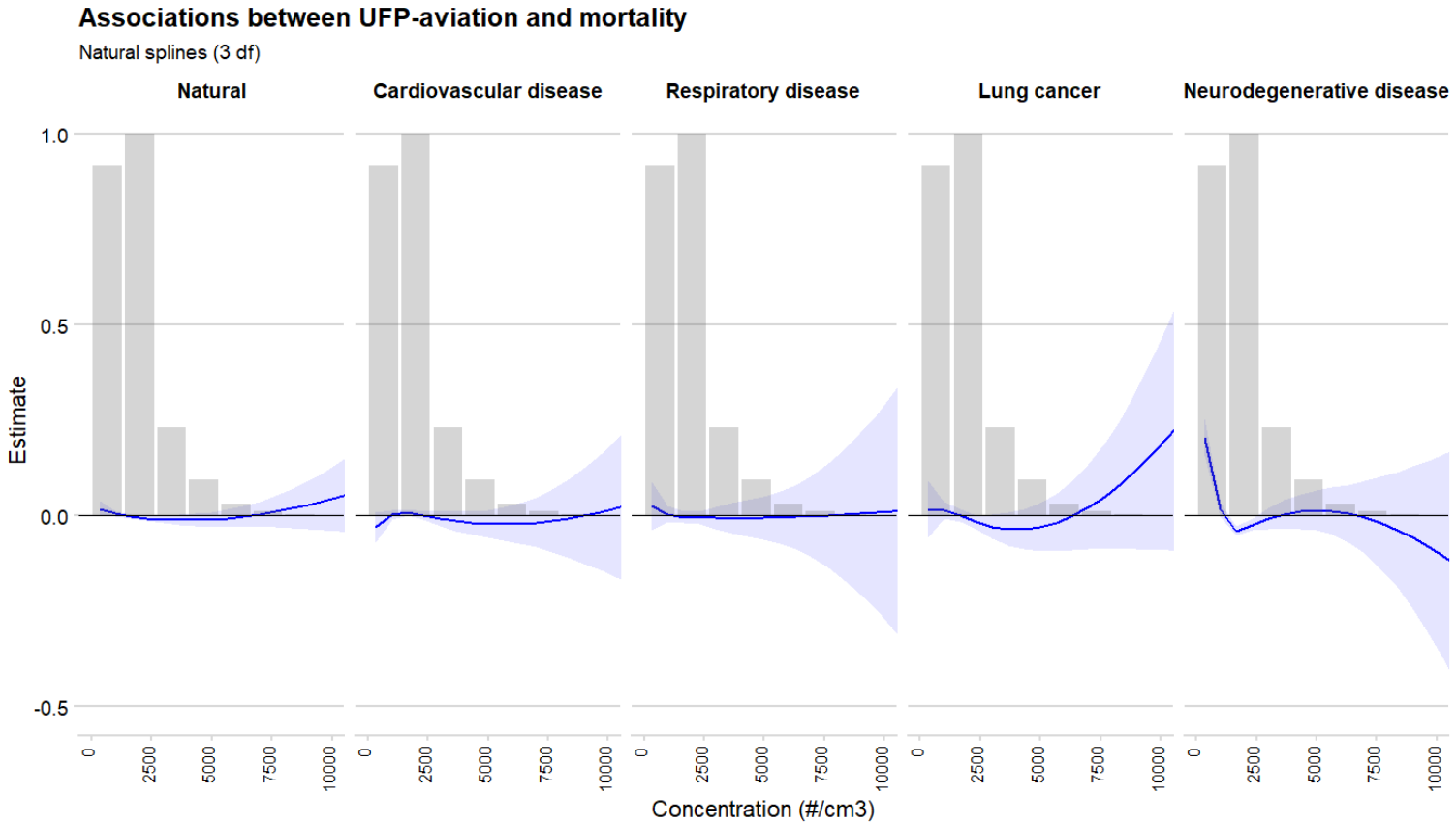


Figure 3.2 Natural cubic splines (3 df) for associations between UFP from aviation and primary mortality outcomes; presentation of concentration limited to 99th percentile of UFP. N=13,726,158. Shaded: 95% confidence intervals. Histogram of exposure added to illustrate sparse data regions.

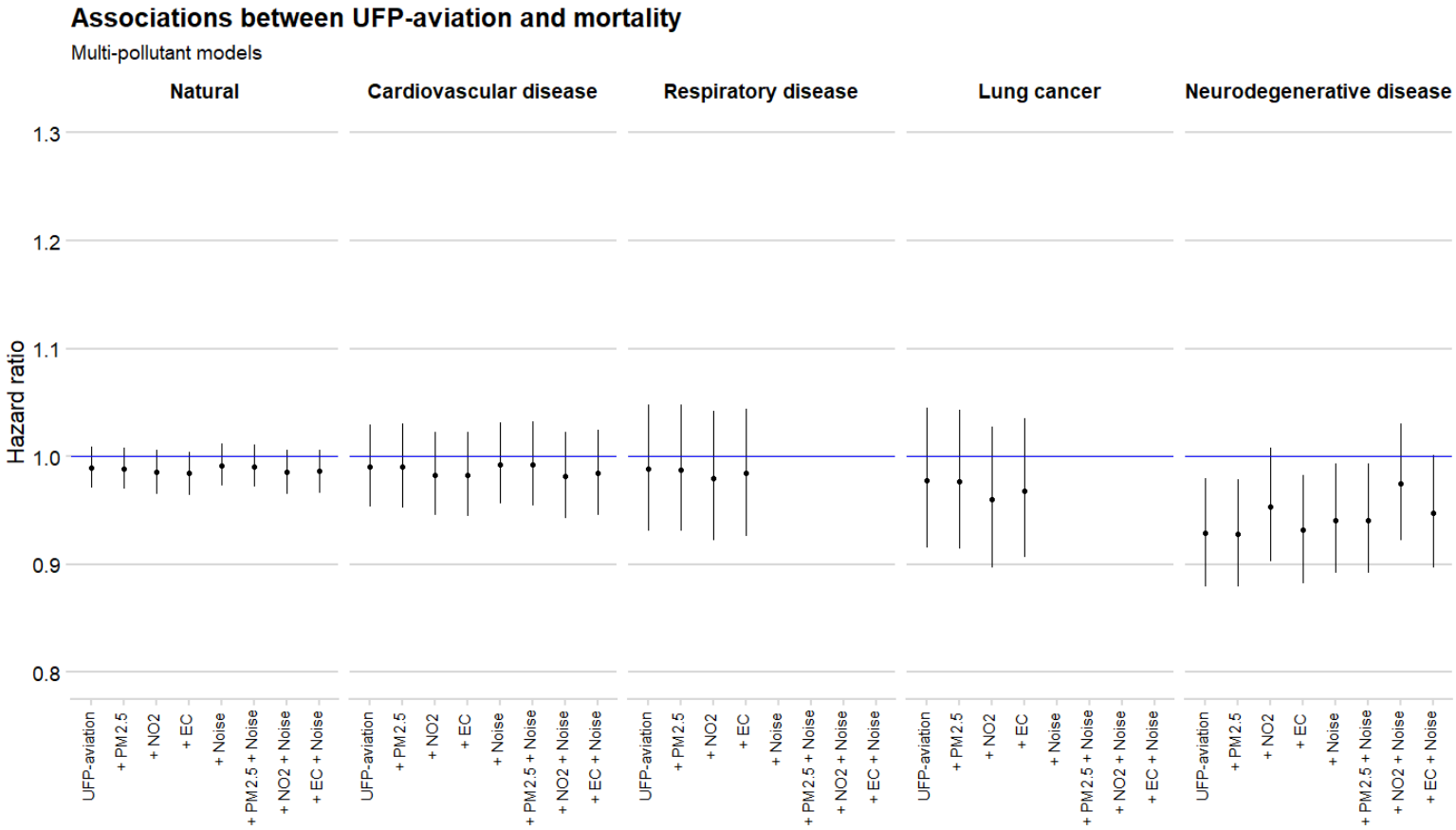


Figure 3.3 Associations between UFP from aviation and primary outcomes in multi-pollutant models. N=13,726,158. Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for 3,500 #/cm^3 increase in UFP.

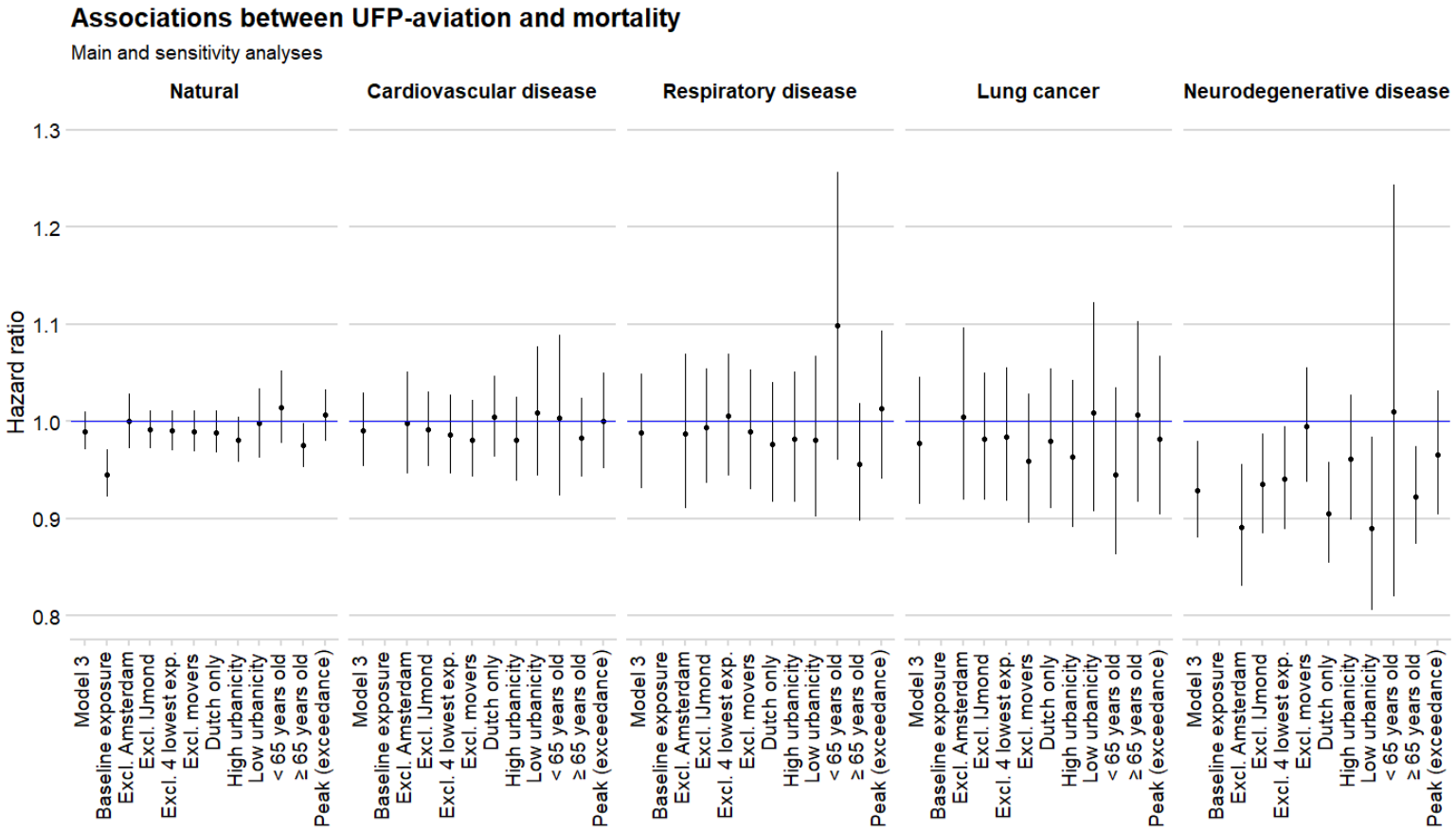


Figure 3.4 Associations between UFP from aviation and primary outcomes in sensitivity analyses. N=13,726,158. Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for 3,500 #/cm^3 increase in UFP.

3.3.5 Associations between UFP from aviation and secondary outcomes

3.3.5.1 Main model

Associations between UFP from aviation and mortality due to arrhythmia, cerebrovascular disease, COPD, diabetes, and Alzheimer's disease were positive in linear analysis, although without reaching statistical significance. Associations for mortality due to ischemic heart disease, myocardial infarction, and stroke were negative, whereas associations for dementia and Parkinson's disease were statistically significantly negative (Table 3.8).

Figure 3.5 (and Figure A.3.2) show the concentration-response functions for UFP and the secondary mortality outcomes. For arrhythmia, associations tended to be steeper at low concentrations, levelling off at high concentrations. As for the curves for neurodegenerative disease mortality, the curves for mortality due to dementia, Alzheimer's disease, and Parkinson's disease were difficult to interpret, as we observed a decreasing trend at the lowest exposures. Additionally, reflecting the differences observed in the linear analysis, the curves for dementia and Alzheimer's disease were very different. Curve shapes for other secondary endpoints were essentially flat.

3.3.5.2 Sensitivity analyses and stratifications

The positive association between UFP from aviation and mortality due to arrhythmia increased and became borderline statistically significant ($p=0.06$) after adjustment for NO_2, and significant at the $p<0.05$ level after further adjusting for noise (Figure 3.6.A). The positive association between UFP from aviation and Alzheimer's disease became statistically significant after adjustment for NO_2 and noise.

When we excluded subjects who lived in Amsterdam a year before baseline or moved there during follow-up, the positive associations between UFP from aviation and arrythmia and diabetes increased and became statistically significant (Figure 3.7.A-3.7.B). For Alzheimer's disease and cerebrovascular disease mortalities, the previously observed positive associations became negative (remaining non-significant).

We found indications of effect modification with respect to age, where the negative associations observed in full population change direction in the group < 65 years for dementia and Parkinson's disease mortality, although with very large confidence intervals reflecting small number of cases (Figures 3.7.A-3.7.B). Also in this subpopulation, the slight positive association for cerebrovascular disease mortality increased, whereas for mortality due to ischemic heart disease or myocardial infarction, the associations became more negative.

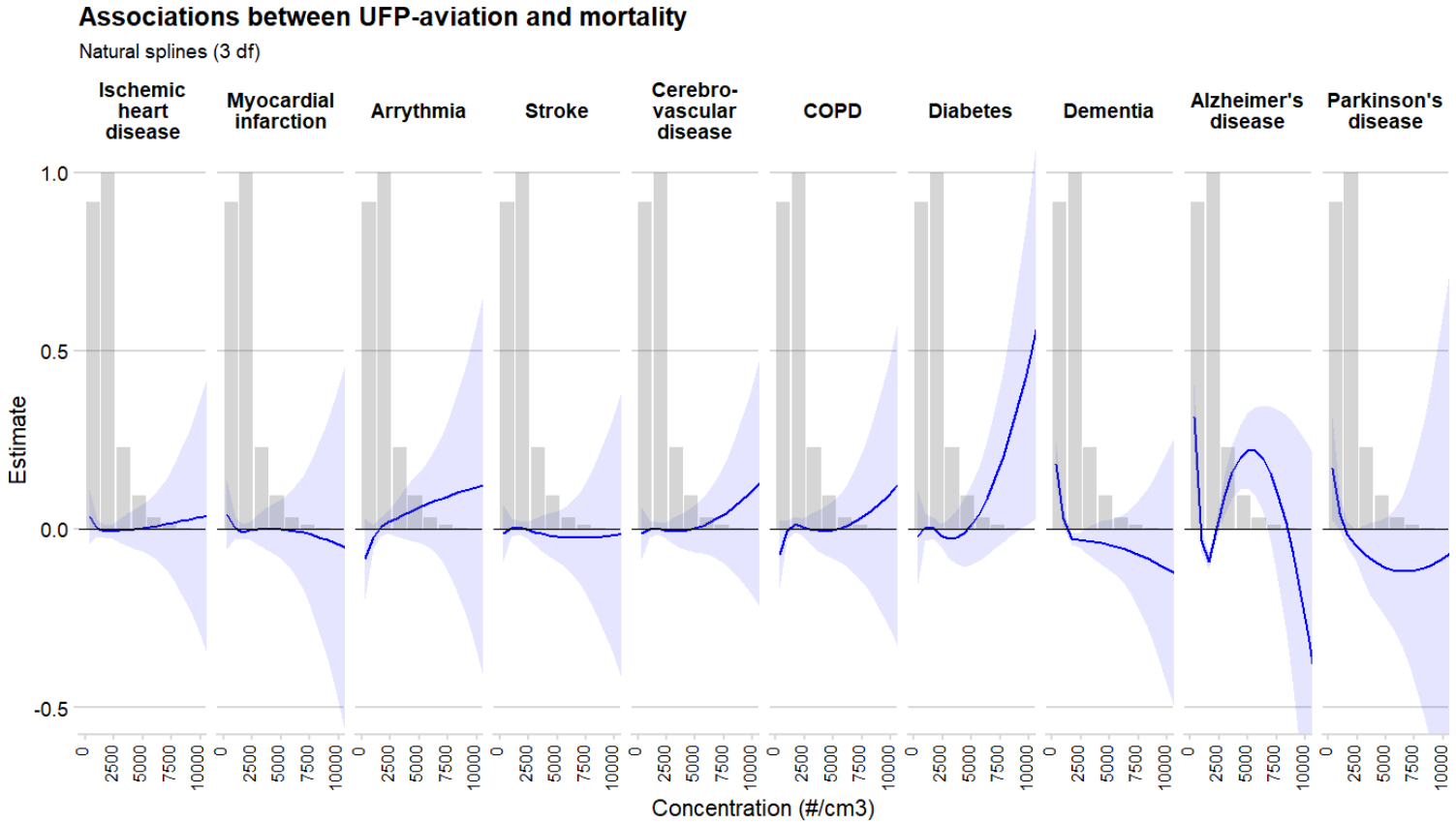


Figure 3.5 Natural cubic splines (3 df) for associations between UFP from aviation and secondary mortality outcomes; presentation of concentration limited to 99th percentile of UFP. N=13,726,158. Shaded: 95% confidence intervals. Histogram of exposure added to illustrate sparse data regions.

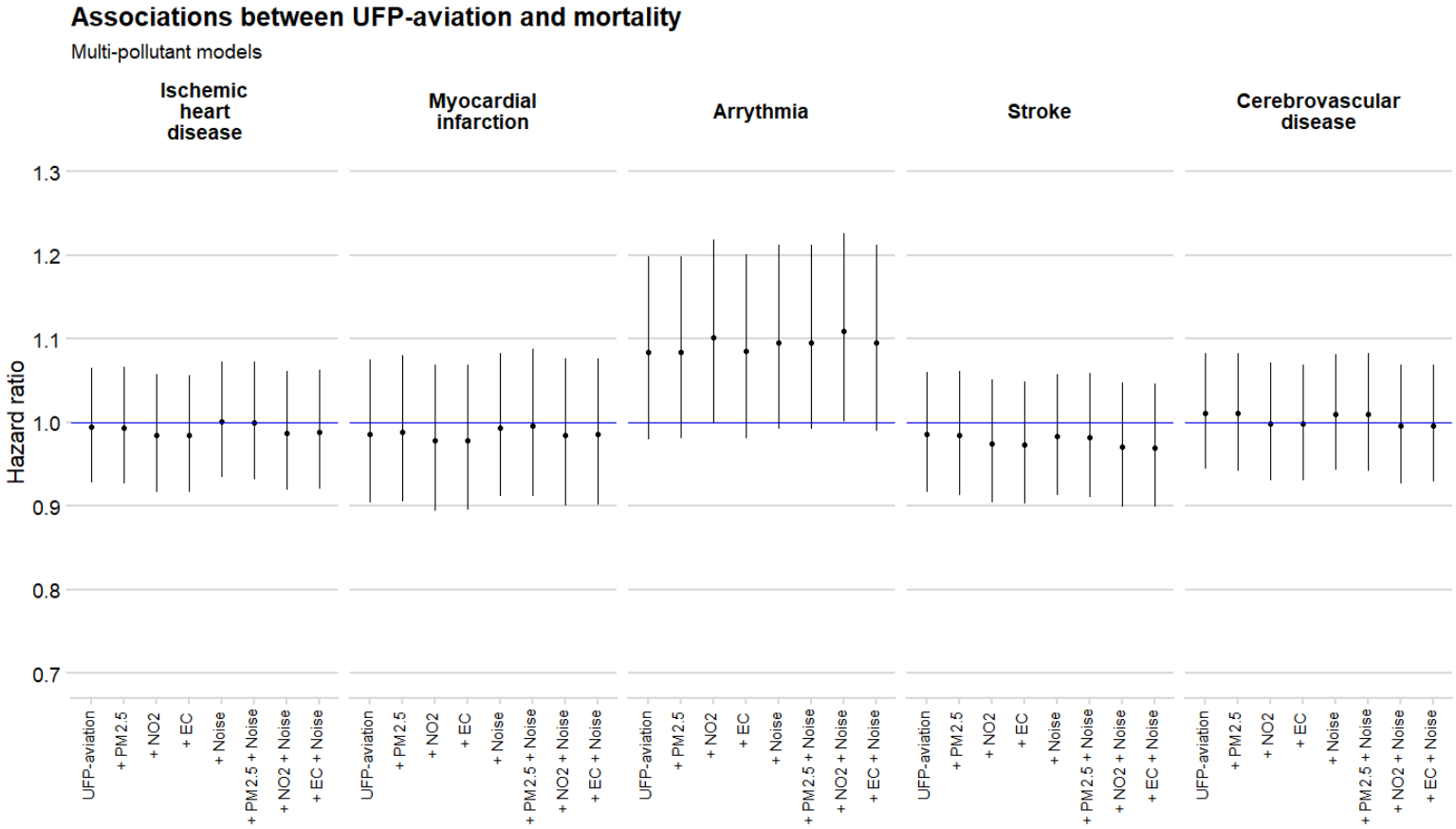


Figure 3.6.A Associations between UFP from aviation and secondary outcomes in multi-pollutant models. N=13,726,158. Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for 3,500 #/cm^3 increase in UFP.

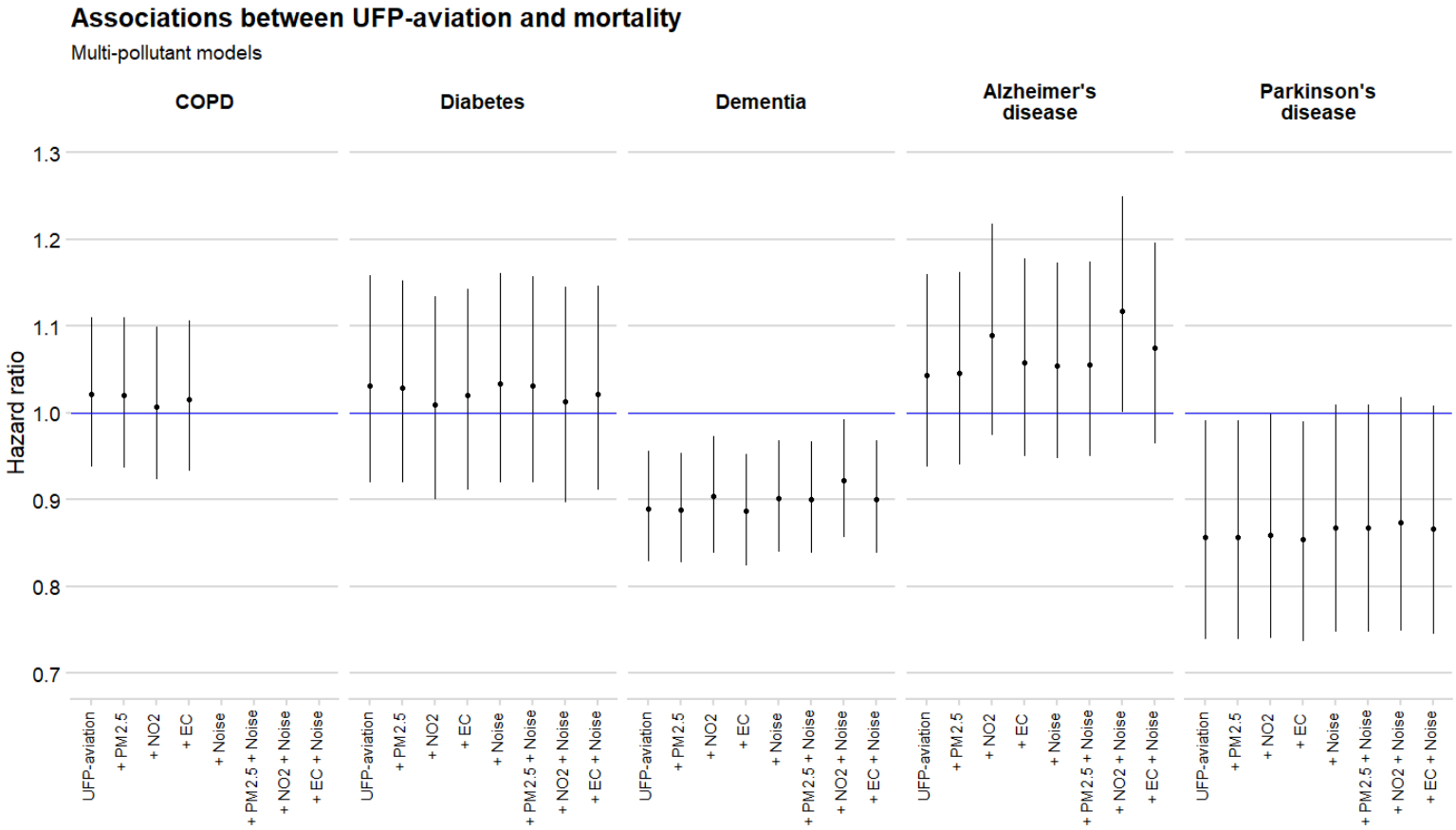


Figure 3.6.B Associations between UFP from aviation and secondary outcomes in multi-pollutant models. N=13,726,158. Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for 3,500 #/cm^3 increase in UFP.

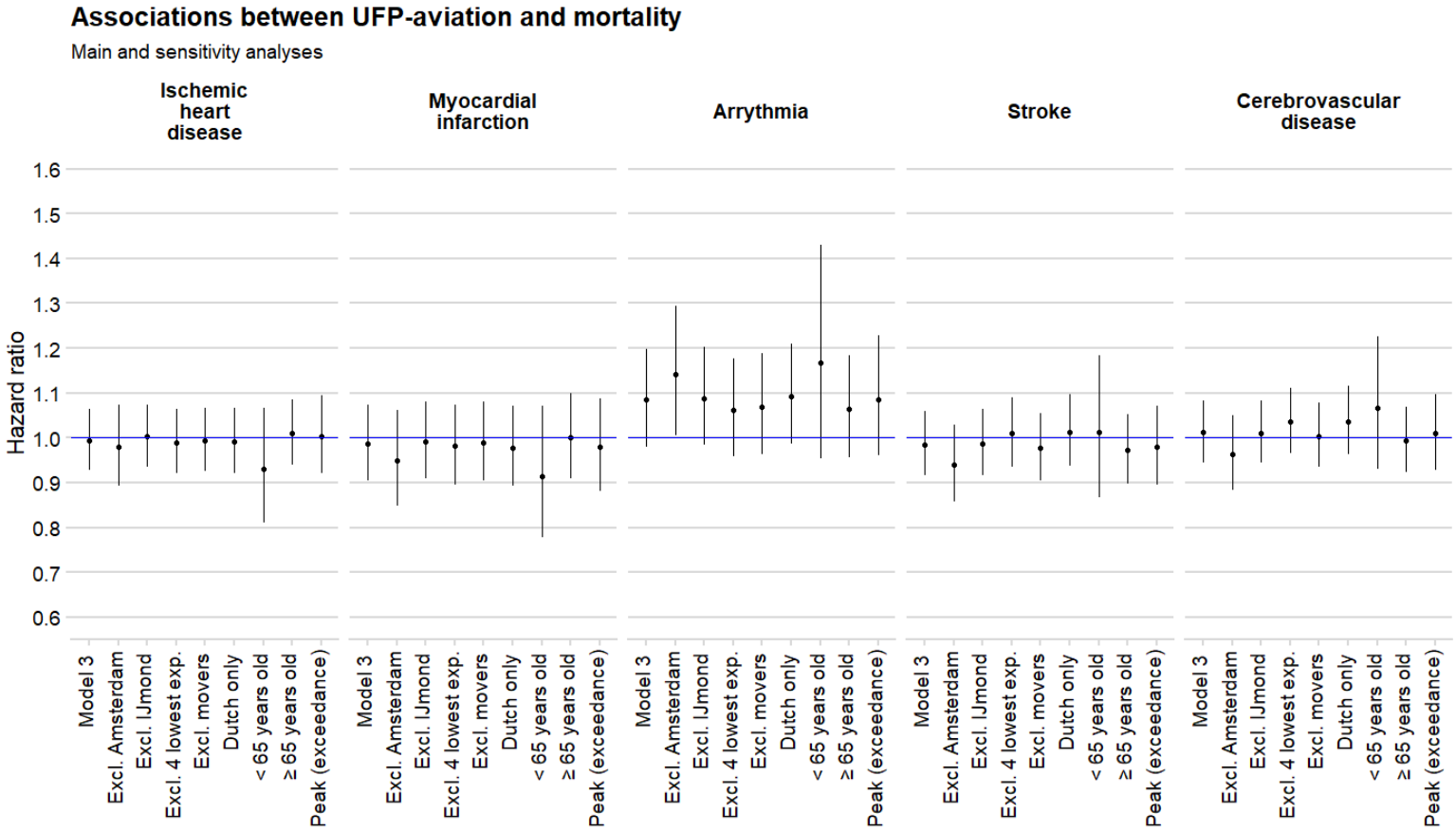


Figure 3.7.A Associations between UFP from aviation and secondary outcomes in sensitivity analyses. N=13,726,158. Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for 3,500 #/cm^3 increase in UFP.

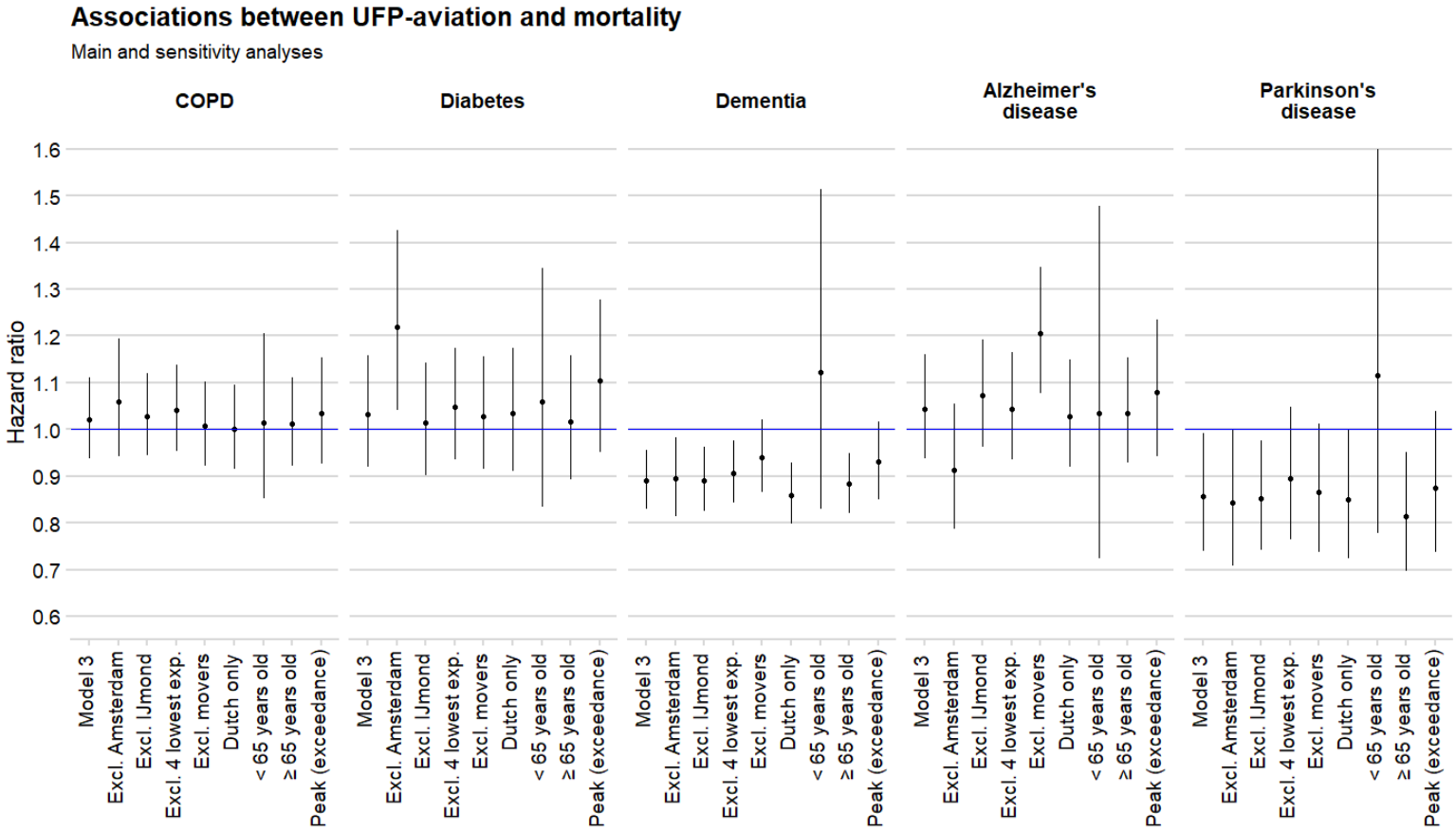


Figure 3.7.B Associations between UFP from aviation and secondary outcomes in sensitivity analyses. N=13,726,158. Hazard ratios (95% confidence intervals) from the main linear model (model 3) presented for 3,500 #/cm^3 increase in UFP.

3.4 Main findings

3.4.1 Summary and classification

In Table 3.11 we present a summary of the results from the main model and the overall classification of the different outcomes, organized by type of effect. The rationale for the classification is described in paragraph 3.4.2.

Table 3.11 Summary of results in the main model and classification of the association, organized by type of effect.

Mortality	HR (95% CI)	Classification
General		
Natural-cause	0.990 (0.971, 1.009)	No association
Cardiovascular		
Cardiovascular disease	0.991 (0.954, 1.029)	No association
Ischemic heart disease	0.995 (0.928, 1.065)	No association
Myocardial infarction	0.986 (0.905, 1.075)	No association
Arrythmia	1.084 (0.980, 1.198)	Probable association
Stroke	0.985 (0.916, 1.060)	No association
Cerebrovascular disease	1.012 (0.944, 1.082)	No association
Metabolic		
Diabetes	1.032 (0.919, 1.158)	No association
Respiratory		
Respiratory disease	0.988 (0.931, 1.048)	No association
Lung cancer	0.978 (0.915, 1.045)	No association
COPD	1.021 (0.938, 1.111)	No association
Neurological		
Neurodegenerative disease	0.929 (0.880, 0.980)	Inverse association
Dementia	0.890 (0.829, 0.956)	Inverse association
Alzheimer's disease	1.043 (0.938, 1.160)	Possible association
Parkinson's disease	0.857 (0.739, 0.992)	Inverse association

N=13,726,158. Primary endpoints in bold.

3.4.2 Rationale for the classification

- We classified as **"no association"** the associations for outcomes related to **natural-cause mortality**, **cardiovascular disease mortality** (incl. separately mortality due to **ischaemic heart disease**, **myocardial infarction**, **stroke**, or **cerebrovascular disease**), and **respiratory disease mortality** (incl. separately mortality due to **COPD** or **lung cancer**). These associations were close to unity, non-significant in the main models, and did not show a clear and consistent pattern of elevated/reduced risk across sensitivity analyses and multi-pollutant models.
- We classified the association for mortality due to **arrythmia** as **"probable association"**. The association was positive in the main model (non-significant) and consistently elevated and robust, (borderline) significant across a number of sensitivity analyses and multi-pollutant models.
- We classified the association for mortality due to **diabetes** as **"no association"**. Effect estimates were generally elevated, but only reached statistical significance in one of the sensitivity analyses (i.e. after excluding Amsterdam). Furthermore, effect estimates reduced towards null after adjustment for NO_2 and EC in two-pollutant models.
- Associations for **Alzheimer's disease mortality** were generally elevated, in some sensitivity analyses reaching (borderline) significance. However, given the unexpected, difficult to interpret shape of its exposure-response function, we decided for the **"possible association"** classification.
- We classified the associations related to **neurodegenerative disease mortality**, and separately for mortality due to **dementia** and **Parkinson's disease** as **"inverse associations"**. These negative, biologically implausible associations, were statistically significant in the main model, and robust across a number of multi-pollutant models and sensitivity analyses (with the exception of population subset < 65 years old, where very little cases were expected and identified).

The associations for dementia and Alzheimer's disease had opposite directions and require careful interpretation. This may be reflected in the nature of the two outcomes, with dementia being a more general term for a decline in mental ability. Visual inspection of the frailty terms for municipality at baseline in a model without exposure showed that there is spatial clustering of diagnoses in favour of one vs. the other outcome. We did adjust for municipality at baseline in our analyses, but that might have not been sufficient. The outcome of additional analysis with Alzheimer's disease mortality combined into dementia mortality (not shown), was nearly identical to separate dementia analysis (dementia had nearly 2.5 times more cases than Alzheimer's disease).

Further interpretation of the observed associations is described in chapter 7.

3.4.3 Study specific aspects

3.4.3.1 Classification of health outcomes

We analysed an extensive number of primary and secondary outcomes based on death certificates. A study in the Netherlands investigating

cause-of-death coding showed high reliability for major causes of death, such as cancers (> 90%), acute myocardial infarction (ICD10: I21; 89%), dementia (F03; 88%), COPD (J40-J47; 85%), ischemic heart disease (I20-I26; 82%), or cerebrovascular disease (I60-I69; 79%). Reliability was low for chronic diseases, such as diabetes (E14; 53%) and atrial fibrillation & cardiac arrythmias (I48-I49; 59%) (Harteloh, 2010). It has to be noted that ICD-10 codes used in that study do not always correspond to grouping of ICD-10 codes used in our study. A likely issue in investigating more specific causes of death is a higher possibility of misclassification. Primary endpoints, for which we specifically chose broad groups of outcomes, are less affected compared to secondary endpoints, as illustrated by discrepancies between dementia (F00-F03) and Alzheimer's disease (G30) in our analysis.

Furthermore, the 2013 manual-to-automatic switch in coding causes of death resulted in substantial changes that affected reporting for some causes of death more than others (Harteloh, 2017). For example, between 2012 and 2013 reporting of vascular dementia (F01) increased by 25%, reporting of unspecified dementia (F03) increased 18%, and reporting of Alzheimer's disease (G30) as a cause of death increased by 30%. All these increases were mostly at the expense of reporting mortality due to pneumonia / airway infections and/or urinary tract infections. Cerebrovascular disease mortality (I60-I69) increased on average 11% between 2012 and 2013, ranging from 12% decrease in subarachnoid haemorrhage (I60) to 220% increase in sequelae of cerebrovascular disease (I69). To address this issue, in all our models the years up to 2012 and from 2013 onward were included in different strata for calendar period (see 3.2.6). Also, we extended our analysis to a cohort with year 2013 as a baseline (see 3.3.4.2).

3.4.3.2 Exposure-response functions

Exposure-response curves generally confirmed the observations from the linear Cox proportional hazards models. Above ca. 7,000 #/cm^3 UFP-aviation, the curves were not very precise (wide confidence intervals), due to scarcity of data in our study period / area (Figures A.3.1 & A.3.2). For all neurodegenerative disease mortality outcomes, we observed unexpected "dips" at low-exposure levels, where decreasing trends were associated with frequently occurring exposures, making the pattern difficult to interpret.

3.4.3.3 Strengths and limitations

Important strengths of our study are a long follow-up time (12 years), a large study population (1.26 million people), and an extensive set of (sensitivity) analyses aimed at checking the robustness of the main model. To limit residual confounding from unmeasured covariates we adjusted for an extensive set of individual- and area-level SES indicators. Our time-varying analysis allowed accounting for time trends in exposure (incl. residential history), area-level SES covariates, and mortality patterns during follow up.

A limitation of the study, due to an administrative nature of our cohort, is that we had limited information on potentially important lifestyle-related indicators. We addressed this limitation by indirectly adjusting natural-mortality risk estimates for smoking and BMI information

obtained from the PHM. We did not observe any indication of noteworthy bias due to absence of adjustment for smoking and BMI in our natural mortality analysis.

3.5 Appendix

Associations between exposure to UFP from aviation and mortality at 2013 baseline

To be able to investigate the associations with endpoints other than natural mortality using baseline exposure (*i.e.*, non-time-varying), we have created a cohort analogous to the full cohort, but with 1-1-2013 as baseline. This cohort was not affected by the change in cause of death coding effective of 2013, but had substantially shorter follow-up time – 8,430,635 person-years-at-risk vs. 13,603,661 in the full cohort.

For natural-cause mortality, the 2013 baseline association was more similar to the time-varying association in the full cohort, than the 2008 baseline association (Table A.3.1). For other endpoints:

- The negative association for lung cancer mortality was no longer present.
- The association for cardiovascular disease mortality became more negative and statistically significant.
- The positive association for arrythmia decreased but remained non-significant positive.
- The association for cerebrovascular disease mortality changed direction and became negative (remaining statistically non-significant).
- The positive association for diabetes became much stronger, although it did not reach statistical significance.
- The association for mortality due to dementia became more negative and statistically significant, whereas the positive association for Alzheimer's disease became much stronger and also reached statistical significance.

Table A.3.1 Risk of death associated with exposure to UFP from aviation in the full cohort and in the 2013 cohort.

Mortality	Full cohort			Cohort 2013	
	Deaths	Time-varying	Baseline	Deaths	Baseline
Natural	185,348	0.990 (0.971, 1.009)	0.945 (0.922, 0.971)	107,097	0.977 (0.951, 1.004)
Cardiovascular disease	47,952	0.991 (0.954, 1.029)	NA	26,623	0.942 (0.894, 0.993)
Respiratory disease	17,460	0.988 (0.931, 1.048)	NA	9,499	0.999 (0.919, 1.086)
Lung cancer	13,802	0.978 (0.915, 1.045)	NA	7,955	1.000 (0.918, 1.089)
Neurodegenerative disease	19,472	0.929 (0.880, 0.980)	NA	12,303	0.955 (0.886, 1.030)
Ischemic heart disease	12,603	0.995 (0.928, 1.065)	NA	6,558	0.986 (0.910, 1.070)
Myocardial infarction	7,775	0.986 (0.905, 1.075)	NA	3,868	0.986 (0.880, 1.106)
Arrythmia	5,330	1.084 (0.980, 1.198)	NA	2,957	1.036 (0.904, 1.188)
Stroke	10,508	0.985 (0.916, 1.060)	NA	5,683	0.987 (0.898, 1.085)
Cerebrovascular disease	12,403	1.012 (0.944, 1.082)	NA	7,143	0.983 (0.897, 1.078)
COPD	8,789	1.021 (0.938, 1.111)	NA	5,118	1.032 (0.915, 1.164)
Diabetes	4,020	1.032 (0.919, 1.158)	NA	2,284	1.115 (0.975, 1.275)
Dementia	11,975	0.890 (0.829, 0.956)	NA	7,386	0.873 (0.785, 0.972)
Alzheimer's disease	4,941	1.043 (0.938, 1.160)	NA	3,332	1.160 (1.009, 1.332)
Parkinson's disease	2,198	0.857 (0.739, 0.992)	NA	1,353	0.847 (0.691, 1.040)

N full cohort time-varying = 13,726,158; N full cohort baseline = 1,259,578; N 2013 cohort baseline = 1,274,325. Primary endpoints in bold. Hazard ratios (95% confidence intervals) presented for 3,500 #/cm^3 increase in UFP. Model 3 included age (as the timescale), sex (strata), calendar period (strata), municipality at baseline (random), marital status, migration background, household income, neighbourhood-level income, percentage of inhabitants with non-western migration background, and percentage of inhabitants with low education.

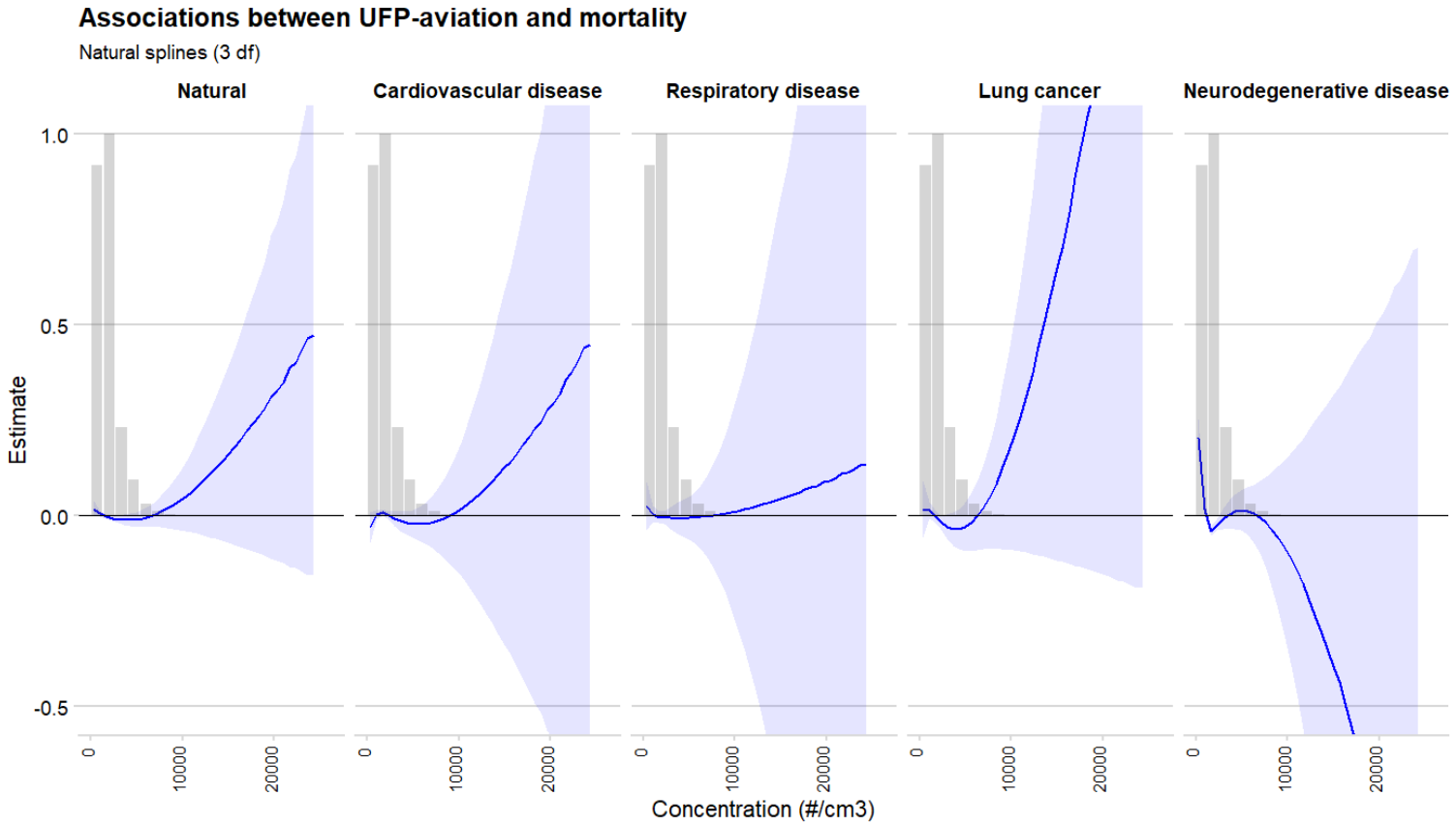


Figure A.3.1 Natural cubic splines (3 df) for associations between UFP from aviation and primary mortality outcomes. N=13,726,158. Shaded: 95% confidence intervals. Histogram of exposure added to illustrate sparse data regions.

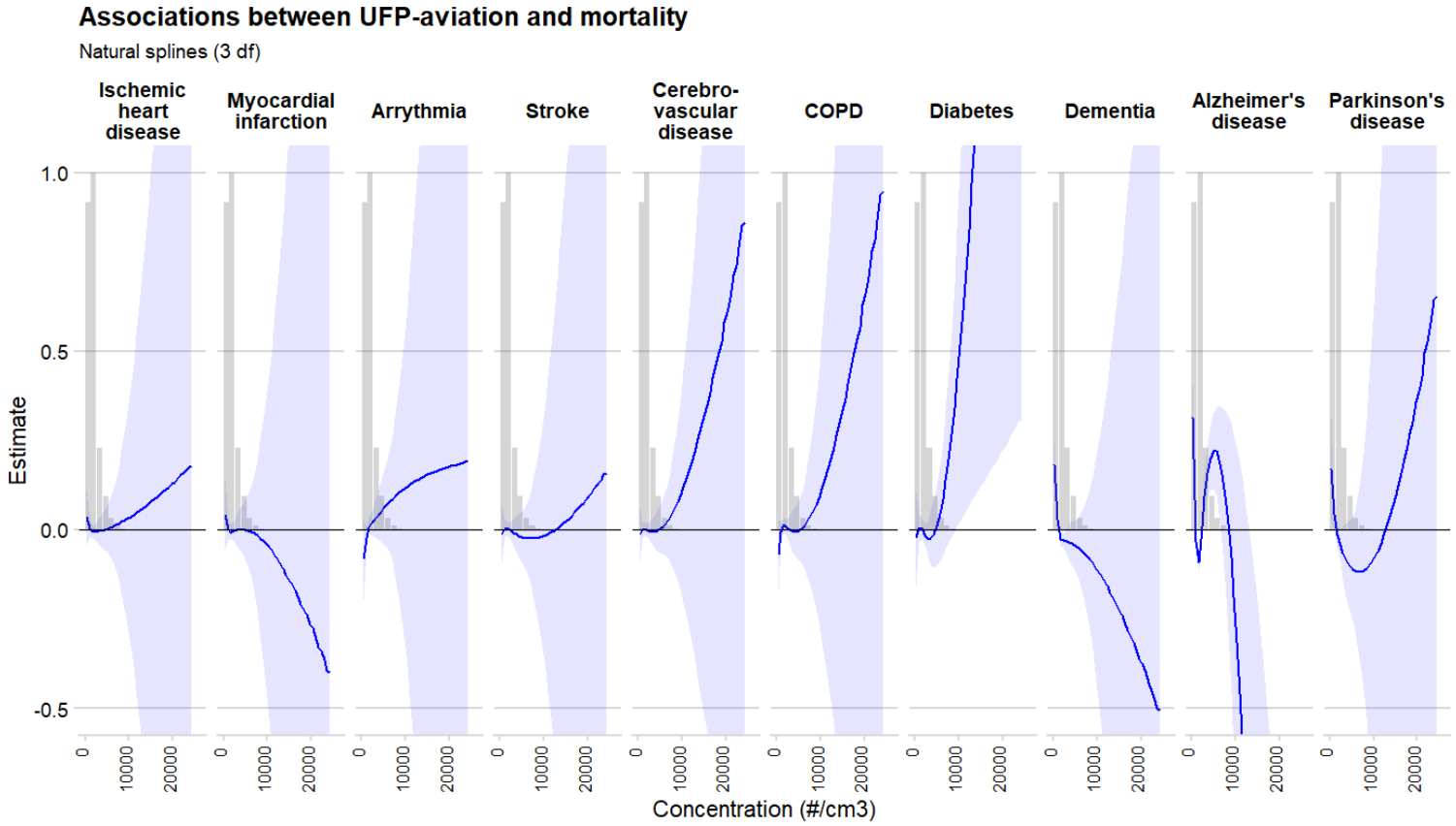


Figure A.3.2 Natural cubic splines (3 df) for associations between UFP from aviation and secondary mortality outcomes. N=13,726,158. Shaded: 95% confidence intervals. Histogram of exposure added to illustrate sparse data regions.

4 Pregnancy outcomes

4.1 Objectives

The main objective is to investigate the association between exposure to UFP from aviation at the residential address during pregnancy and pregnancy outcomes.

The specific objectives of this study are:

1. To investigate the associations between exposure to UFP from aviation during pregnancy and low birth weight, preterm birth and small for gestational age during the study period 2006-2018 (primary health endpoints).
2. To explore associations between exposure to UFP from aviation during pregnancy and mortality before age 1, including stillbirth, congenital anomalies and Apgar score during the study period of 2006-2018 (secondary health endpoints).

4.2 Methods

4.2.1 Study population

The present study includes information from pregnancies in the Schiphol study area from 2006 through 2018.

The cohort was constructed by extracting and merging anonymized data from the Perinatal Registration Netherland (PRN) to individual data from other registrations, which were accessed and linked by a secured working environment at CBS. More details of the CBS datasets used can be found in paragraph 2.6.

The PRN-database includes pregnancy and birth data that are registered by the four groups of health professionals that provide perinatal care: midwives, general practitioners, gynaecologists and paediatricians/neonatologists. The registration is managed by Perined on behalf of their four professional associations: the KNOV (Royal Netherlands Organisation of Midwives), the LHV (National General Practitioners Association, including the obstetrically active general practitioners united in the VVAH), the NVOG (Dutch Association for Obstetrics and Gynaecology) and the NVK (Dutch Association for Paediatrics). The PRN database covers approximately 95% of all births in the Netherlands in the period from 2004 to 2018.

The PRN-database was available at CBS and comprises data on mother-infant pairs, for which mothers are registered at the municipal basic registration (GBA - Gemeentelijke Basis Administratie) and infants have a gestational age of 22 weeks (154 days) or more at birth.

The PRN-database was enriched with data from several databases from CBS, including individual covariates (such as maternal age, marital status, region of origin, standardized household income and maternal education), neighbourhood-level socio-economic status covariates and address history. After permission of Perined also information regarding congenital anomalies was obtained.

4.2.2 *Inclusion and exclusion criteria*

For this study we selected all mother-infant pairs for whom birth occurred between 1-1-2006[8] and 31-12-2018 and who had lived in the study area for at least six months of the pregnancy, or during the full pregnancy in case of a pregnancy period < 6 months. For analyses related to the primary outcomes and Apgar scores, only livebirths were included.

We excluded multiple births, mothers ≤16 years of age at birth, mothers with incomplete residential history during pregnancy or mothers who changed address more than once during pregnancy. This results in a total of 287,167 births, of which 285,809 were live births.

For the analyses on low birth weight and Apgar-scores also preterm deliveries (GA<37 weeks), were excluded, which resulted in a total of 270,553 live births.

4.2.3 *Pregnancy outcomes*

Gestational age (GA), defined as the number of days between the start of the last menstruation and birth, and birth weight, in grams, was obtained from the PRN database and were used to define the **primary health outcomes** of interest:

- Small for gestational age (SGA): birthweight <10th percentile based on prescriptive sex-specific birthweight charts described by Hoftiezer et al (2018).
- Low Birth Weight (LBW): Weight at term (≥37weeks gestation) birth below 2500 grams.
- Preterm birth:
  - Preterm birth: < 37 weeks/260 days of gestation.
  - Moderately preterm birth: between 30 and 36 weeks/230-259 days of gestation.
  - Severe preterm birth: < 30 weeks/230 days of gestation.

All primary health outcomes were defined as a binary variable (yes/no and (moderately/severe) preterm vs. term birth).

Secondary health outcomes of interest were:

- Mortality - a binary variable defined as:
  - Infant mortality; still births and infant mortality within the first year of life.
  - Foetal mortality; stillbirth/ mortality during labour.
  - Perinatal mortality: stillbirths and mortality in the first week of life.
  - Neonatal mortality; mortality of a live-born before 28 days of age.
  - Post-neonatal death; death of an infant between 28 days and 1yr of age.
- Congenital anomalies - a binary variable defined as:
  - Nervous and senses system (Q00-Q18).
  - Circulatory system (Q20-Q28)
  - Respiratory system (Q30-Q34)

[8] data from 2004-2005 were excluded at forehand because of high frequency (>50%) of missing information on maternal education

  - Digestive system (Q35-Q45)
  - Urogenital system (Q50-Q64)
  - Musculoskeletal system (Q65-Q79)
  - Skin and abdominal wall (Q80-Q82)
  - Any of the congenital anomalies reported above.
- Apgar score at 5 minutes:
  - Categorized in three ordinal groups; low (0-6), intermediate (7,8) and reference (9,10).
  - Low Apgar vs 9,10.
  - Intermediate Apgar vs 9,10.

4.2.4 Potential confounders

See also paragraph 2.6.

(Individual-level) covariates from the PRN-database that were considered in the analyses include:

- Sex of the baby (male, female).
- Year of birth (2006-2018)Month of birth (1-12).
- Parity (primipara, multipara).
- Maternal age at delivery (5 categories; <20, 20-29, 30-34, 35-39, =>40 years).
- Gestational age (in weeks; when low birth weight, mortality or Apgar -score was the outcome of interest).
- Birth weight (when mortality or Apgar-score was the outcome of interest).

(Individual-level) covariates from other datasets at CBS include:

- Maternal highest level of education at the year of birth (low, middle, high).
- Maternal standardized household income at the year of birth (10 categories; <p1, p1-5, p5-10, p10-25, p25-50, p50-75, p75-90, p90-95, p95-99, >p99).
- Marital status mother at the year of birth (3 categories; Married/living together, unmarried/never married, divorced / widowed).
- Maternal migration background (7 categories: Dutch, Netherlands Antilles, Suriname, Morocco, Turkey, Other Western, Other non-Western).

The following area level covariates, provided by CBS, were included:

- Percentage inhabitants with high educational level (in quintiles).
- Percentage of inhabitants with a non-western country of origin (in quintiles).

4.2.5 Exposure to UFP, co-pollutants and noise

General information on the exposure assessment in the Schiphol area can be found in paragraph 2.5 and paragraph 2.7.

Information about UFP from aviation at the residential address was available as monthly averages, for all months in the period 2003-2018. We consider exposure during the full pregnancy (~9 months) as our primary exposure window. In addition, we considered the 3 months before pregnancy (T0), each of the three trimesters of pregnancy (T1, T2 and T3) and the total period (~12 months) as additional/secondary

exposure windows. For each month a subject lived outside the study area, an average UFP value of 0 #/cm^3 was assigned.

For PM2.5, PM10, NO_2 and EC, only annual average concentrations were available for each address. We used the temporal variation of concentrations at the regional and urban background measurement stations of the Dutch National Air Quality Monitoring Network in the study area to derive moving 3 monthly average concentrations from the annual average air pollution concentrations.

For birth defects the second month was considered at the most relevant exposure period (Vrijheid, 2011) and was used as primary exposure window. We also considered the three months before conception (T0), the first trimester (T1) and the (6-month) average of T0 and T1 as additional exposure window.

4.2.6 Statistical analyses

4.2.6.1 Missing data

Approximately 23% of the birth records had missing data on maternal education or household income. We replaced missing values by using multiple imputation by chained equations (MICE) (van Buuren and Groothuis-Oudshoorn, 2010) to generate 5 datasets using 5 iterations. All variables that were available and could potentially predict maternal education or household income were used in the imputation procedure, and include maternal age at delivery, parity, maternal education, household income, marital status, migration background, area level education, area level household income, area level unemployment rate, area level social assistance and the percentage people with a non-western background.

4.2.6.2 Main analyses

After exploring descriptive statistics, frequency tables and correlations of UFP-aviation exposure, co-pollutants, noise, other covariates and pregnancy outcomes, associations between UFP from aviation and pregnancy outcomes were studied with logistic regression.

As described in paragraph 2.8.2 we defined several models with increasing covariate adjustment. For the pregnancy outcomes this resulted in following single-pollutant models:

- Model 1: adjusted for sex of the baby, parity, gestational age (only for low birth weight, Apgar and mortality as outcome) and low birth weight (only for Apgar and mortality as outcome).
- Model 2: Model 1 + maternal household income, maternal educational level, maternal marital status, maternal age at delivery and maternal region of origin.
- Model 3: Model 2 + percentage inhabitants with high education at area level and percentage inhabitants with a non-Western origin at area-level.

Models 1 and 2 were selected **a priori**.

For the selection of the area-level SES indicators in model 3, we considered the covariates of model 2 as the basic model. Next, we added each area-level indicator (categorized in quintiles) and with

forward stepwise regression evaluated the model fit. We used the Akaike Information Criteria (AIC) to select the model with the best fit. This resulted in including the percentage of inhabitants with a high education and percentage with non-western background as indicators for area SES.

We evaluated the shape of the exposure-response curves by using natural splines with 3 degrees of freedom.

4.2.6.3 Multi-pollutant models
See paragraph 2.10.1

4.2.6.4 Sensitivity analyses and stratifications
We performed the following analyses to study the robustness of the results and to study associations in subgroups (for rationale: see paragraph 2.10.2):

- Exclusion of mothers who moved during pregnancy.
- Adjusting for urbanization (5 categories).
- Stratification for urbanization (2 strata: 1+2 and ≥3).
- Exclusion of mothers who lived in the municipality of Amsterdam at the date of either conception or birth.
- Exclusion of three municipalities (Velsen, Beverwijk and Heemskerk) around a major industrial source in the IJmond region.
- Limiting the statistical analysis to participants with a Dutch background.
- Evaluate peak exposure to UFP from aviation by using the %hours above 66,667 #/cm^3 (instead of an annual average concentration)[9].
- Exclusion of birth records with imputed data (complete case analyses).
- Exclusion of infant mortality (<1st year of age).
- Stratification for maternal education (3 strata: low, medium and high).
- Exclude elective Caesarean sections and labour inductions.
- Exclude gestational age as confounder (Low birth weight).
- Exclude children with birth defects (only for infant mortality and Apgar scores).
- Stratification for normal and low birth weight (only for infant mortality).
- Stratification for exposure per trimester (T1, T2 and T3), the three months prior conception (T0) and the full pregnancy including pre-conception (5 strata).
- Stratification for exposure during T0, T1 and the 6-month average of T0 and T1 (3 strata; only for birth effects).
- Stratification for birth year (two strata: born before January 1st 2013, born on January 1st 2013 or later).
- Excluding the four municipalities with the lowest average UFP-exposure.
- Including a random intercept for municipality, as an indicator of health care provider.

[9] *Due to rescaling of the UFP-exposure the peak-threshold is set on 2/3 of 100,000#/cm^3.*

4.3 Results

4.3.1 Study population

Table 4.1 presents population characteristics for all live births, all births as well as for complete cases. About 23% of the observations had missing values in maternal education (19%) and/or household income (5%). The other individual covariates did not have any missing values. The dataset with only complete cases included a somewhat lower proportion of married mothers (51.8% vs 54.0%) and higher percentage of mothers of Dutch origin (60.8% vs 57.5%). The latter is probably explained by a higher proportion of missing information on education in subjects of non-Dutch origin.

Table 4.1 Characteristics of the study population.

Individual Covariates	All live births (n=285,809) N (%)	Live births, complete cases (n=221,156) N (%)	All births (n=287,167) N (%)	All births, complete cases (n=222,164) N (%)
Male	146,460 (51.2)	113,424 (51.3)	147,175 (51.3)	113,953 (51.3)
Female	139,349 (48.8)	107,732 (48.7)	139,992 (48,7)	108,211 (48,7)
Parity				
1	134,980 (47.2)	105,909 (47.9)	135,684 (47.2)	106,434 (47.9)
≥2	150,829 (52.8)	115,247 (52.1)	151,483 (52.8)	115,730 (52.1)
Maternal age at delivery				
≤ 19	2,273 (0.8)	2,004 (0.9)	2,290 (0.8)	2,019 (0.9)
20-29	70,496 (24.7)	56,258 (25.4)	70,822 (24.8)	56,510 (25.6)
30-34	110,600 (38.7)	86,565 (39.1)	111,076 (38.9)	86,922 (39.3)
35-39	88,926 (31.1)	66,865 (30.2)	89,382 (31.3)	67,192 (30.4)
≥ 40	13,514 (4.7)	9,464 (4.3)	13,597 (4.8)	9,521 (4.3)
Marital status				
Married/living together	154,353 (54.0)	114,626 (51.8)	155,041 (54.0)	115,119 (51.8)
Unmarried/never married	122,357 (42.8)	99,853 (45.2)	122,963 (42.8)	100,328 (45.2)
Divorced/widowed	9,099 (3.2)	6,677 (3.0)	9,163 (3.2)	6,717 (3.0)
Migration background				
Dutch	164,383 (57.5)	134,391 (60.8)	165,061 (57.5)	134,931 (60.7)
Netherlands Antilles	3,231 (1.1)	2,805 (1.3)	3,253 (1.1)	2,823 (1.3)
Suriname	14,796 (5.2)	12,470 (5.6)	14,919 (5.2)	12,567 (5.7)
Turkey	13,875 (4.9)	10,568 (4.8)	13,949 (4.9)	10,622 (4.8)
Morocco	23,249 (8.1)	17,756 (8.0)	23,395 (8.2)	17,865 (8.0)
Other, western	38,722 (13.6)	24,450 (11.1)	38,873 (13.6)	24,531 (11.0)
Other, non-western	27,553 (9.6)	18,716 (8.5)	27,717 (9.7)	18,825 (8.5)
Maternal education				
Low	42,193 (14.8)	39,608 (17.9)	42,480 (14.8)	39,871 (18.0)
Medium	68,201 (23.9)	65,338 (29.5)	68,509 (24.0)	65,632 (29.5)
High	120,994 (42.3)	116,210 (52.6)	121,462 (42.5)	116,661 (52.5)
Missing	54,421 (19.0)		54,716 (19.1)	
Household income[1]				
≤ 1 percentile	1,644 (0.6)	1,269 (0.6)	1,655 (0.6)	1,277 (0.6)
>1-5 percentile	6,731 (2.4)	5,434 (2.5)	6,765 (2.4)	5,462 (2.5)
>5-10 percentile	17,493 (6.1)	14,231 (6.4)	17,607 (6.1)	14,330 (6.5)
>10-25 percentile	29,295 (10.3)	22,636 (10.2)	29,456 (10.3)	22,754 (10.2)
>25-50 percentile	47,182 (16.5)	35,667 (16.1)	47,405 (16.5)	35,837 (16.1)
>50-75 percentile	65,661 (23.0)	52,451 (23.7)	65,959 (23.0)	52,683 (23.7)
>75-90 percentile	52,675 (18.4)	44,952 (20.3)	52,903 (18.4)	45,129 (20.3)

Individual Covariates	All live births (n=285,809) N (%)	Live births, complete cases (n=221,156) N (%)	All births (n=287,167) N (%)	All births, complete cases (n=222,164) N (%)
>90-95 percentile	23,741 (8.3)	20,712 (9.4)	23,843 (8.3)	20,793 (9.4)
>95-99 percentile	23,316 (8.2)	20,216 (9.1)	23,408 (8.2)	20,296 (9.1)
>99 percentile	4,352 (1.5)	3,588 (1.6)	4,374 (1.5)	3,603 (1.6)
Missing	13,719 (4.8)		13,792 (4.8)	

[1] Percentile of the distribution in the whole Netherlands.

4.3.2 Health outcomes

Table 4.2 presents the prevalence of the selected health endpoints. We observed 4,287 (1.6%) live births with low birth weight at full term. 15,140 live births (5.3%) were premature, of which 1,335 (8.8%) were severely premature (<30 weeks). About 10% of all live births were small for gestational age (SGA).

Infant mortality was about 0.8% (2,164 cases), of which about 63% were stillbirths or occurred during birth. We decided to only include total infant mortality (up to the first year of life) and to not to make any distinctions in the time of mortality occurred.

For congenital anomalies, anomalies in the circulatory (1,045 cases) and uro-genital system (1,119 cases) were the most frequent.

Apgar scores were available for 99.9% of all live births. A maximum score of 10 was reported in 79.3% of all livebirths, 93.4% had an Apgar of 9 or 10 (reference category), 5.1% had an Apgar score of 7 or 8 and 1.5% had an Apgar score below 7.

Table 4.2 Prevalence of selected health outcomes in the study population (outcomes that are only presented for descriptive purpose, and not included in the analyses are indicated in grey).

Pregnancy Outcomes	All live births (n=285,809) N (%)	Live births, complete case (n=221,156) N (%)	All births (n=287,167) N (%)	All births, complete case (n=222,164) N (%)
Primary outcomes				
Birth weight (g); mean (sd)[1]	3,446 (556)	3,448 (555)	3,436 (578)	3,439 (576)
Low birth weight (<2,500 g at full term)[2]	**4,287 (1.6)**	**3,283 (1.6)**	4,329 (1.6)	3,309 (1.6)
Gestational age (weeks)[1]	39 (2)	39 (2)	39 (2)	39 (2)
Prematurity (<37 weeks)	**15,140 (5.3)**	**11,666 (5.3)**	16,191 (5.6)	12,452 (5.6)
- **Severe prematurity (<30 weeks)**	1,335 (0.5)	1,010 (0.5)	2,110 (0.7)	1,599 (0.7)

Pregnancy Outcomes	All live births (n=285,809) N (%)	Live births, complete case (n=221,156) N (%)	All births (n=287,167) N (%)	All births, complete case (n=222,164) N (%)
- **Moderate prematurity (30-36 weeks)**	13,805 (4.8)	10,656 (4.8)	14,081 (4.9)	10,853 (4.9)
SGA-Small for gestational age[2]	**28,996 (10.2)**	**21,999 (10.0)**	29,639 (10.3)	22,467 (10.1)
Secondary outcomes				
Mortality before age 1				
Infant mortality: 1st year	806 (0.3)	593 (0.3)	2,164 (0.8)	1,601 (0.7)
Fetal mort.: stillbirth/during labor	N.A.	N.A.	1,358 (0.5)	1,008 (0.5)
Perinatal mortality: still births & mortality< 7 days	592 (0.21) 721 (0.25) 85 (0.03)	443 (0.20) 533 (0.24) 60 (0.03)	1,950 (0.68) 721 (0.25) 85 (0.03)	1,451 (0.65) 533 (0.24) 60 (0.03)
Neonatal mortality: day 1-28				
Postnatal mortality: day28- 1 year				
Apgar scores (5 min)				
<7	4,179 (1.5)	3,238 (1.5)		
7,8	14,575 (5.1)	11,295 (5.1)		
9,10	266,915 (93.4)	206,516 (93.4)		
missing	140 (0.1)	107 (0.1)		
Congenital anomalies (ICD10)				
1. Nervous and senses system (Q00-Q18)	465 (0.16)	380 (0.17)	518 (0.18)	418 (0.19)
2. Circulatory system (Q20-Q28)	1,008 (0.35)	776 (0.35)	1,045 (0.36)	804 (0.36)
3. Respiratory system (Q30-Q34)	621 (0.22)	479 (0.22)	635 (0.22)	487 (0.22)
4. Digestive system (Q35-Q45)	218 (0.08)	158 (0.07)	222 (0.08)	160 (0.07)
5. Urogenital system (Q50-Q64)	1,109 (0.39)	869 (0.39)	1,119 (0.39)	878 (0.40)
6. Skin and abdominal wall (Q80-Q82)	564 (0.20)	454 (0.21)	566 (0.20)	456 (0.21)
7. Muscolo-skeletal system (Q65-Q79)	917 (0.32)	703 (0.32)	945 (0.33)	725 (0.33)
8. Any of the studied congenital anomalies	4274 (1.50)	3321 (1.50)	4409 (1.54)	3422 (1.54)

[1] Only included for descriptive purposes, not analysed as a continuous variable; included as covariate in part of the analyses; [2] At ≥ 37 weeks of gestation, n=270,669; [3] Small for gestational age defined as birth weight below the 10th percentile.

4.3.3 Exposure

4.3.3.1 Distribution of UFP from aviation, other air pollutants and noise

The average residential exposure to UFP from aviation during pregnancy was about 1,900 #/cm^3 (table 4.3). Variation was larger for UFP from aviation as compared to the other air pollutants or noise. About 10% of the mothers were exposed to average concentrations of UFP from aviation above 3,200 #/cm^3 during pregnancy.

The proposed cut-off value of 53 dB (Lden) for noise (see paragraph 2.7.2) was exceeded in <5% of the observations for aviation noise from Schiphol and noise from rail traffic (p95 < 53db) and around 50% of the observations for noise from road traffic.

4.3.3.2 Correlation between UFP from aviation, other exposures and neighbourhood SES

Table 4.4 presents Spearman correlation coefficients between UFP from aviation, other air pollutants, noise and indicators for neighbourhood SES.

UFP from aviation was poorly correlated with most of the other exposure and indicators for area-level SES. The highest correlation was observed with aviation noise from Schiphol (R=0.42); all other correlation coefficients were <0.1.

As summarised in paragraph 2.10.1.1, average residential concentrations of the co-pollutants (PM2.5, NO_2 and EC) were highly correlated.

Between the different indicators for area-level SES, a high negative correlation is observed between %high and %low education R~-0.9) and between mean income and low education (R~0,8). A high positive association is observed between mean income and %high education (R~0.7) and between %non-western and social assistance (R~0.8).

4.3.3.3 Distribution of UFP from aviation per degree of urbanisation

Table 4.5 presents the distribution of UFP from aviation for the different categories of degree of urbanisation. About 54% of the population lived in a highly urbanized neighbourhood (>2,500 addresses/km^2). We observed no clear pattern of increasing or decreasing UFP concentrations with degree of urbanisation.

Table 4.3 Distribution of UFP from aviation, other air pollutants and noise; all pregnancies (n=287,167) (UFP in #/cm³; other air pollutants in µg/m³, noise in dB (Lden)).

	Mean	sd	p1	p5	p10	p25	p50	p75	p90	p95	p99
UFP-aviation											
During pregnancy	1,857	1,103	599	744	864	1,141	1,549	2,215	3,224	4,125	5,877
Trimester 1	1,848	1,238	345	617	777	1,061	1,517	2,227	3,331	4,313	6,527
Trimester 2	1,861	1,249	385	632	785	1,065	1,521	2,240	3,357	4,367	6,580
Trimester 3	1,861	1,257	316	615	773	1,060	1,524	2,247	3,373	4,372	6,633
3 months before	1,853	1,247	297	613	777	1,063	1,523	2,233	3,347	4,343	6,542
Total (i.e., ~12 months)	1,856	1,081	641	755	869	1,153	1,554	2,216	3,213	4,109	5,757
Peak exposure: # hrs/month above 66,667 #/cm3[1]	82	70	12	18	23	37	59	105	169	226	346
Other air pollutants[2]											
PM2.5	14.9	2.9	10.0	10.8	11.4	12.7	14.6	17.2	19.0	19.9	21.7
NO_2	27.5	5.3	16.3	19.1	20.8	23.8	27.3	31.0	34.6	36.7	40.7
EC	1.1	0.4	0.6	0.7	0.7	0.9	1.1	1.4	1.7	1.8	2.2
PM2.5-EC	13.8	2.6	9.3	10.0	10.6	11.8	13.5	15.8	17.5	18.2	19.7
Noise[1]											
Aviation (Schiphol)	44.7	3.3	38.7	40.0	40.8	42.4	44.5	46.7	49.1	50.6	54.3
Rail traffic	36.2	8.8	24.0	24.0	24.0	30.3	35.2	41.8	48.6	52.7	59.4
Road traffic	54.0	6.3	41.0	44.4	46.2	49.4	53.6	58.3	62.6	65.1	69.3

[1] Due to rescaling of the UFP-exposure the peak-threshold is set on 2/3 of 100,000#/cm³.
[2]During pregnancy.

Table 4.4 Spearman correlation between UFP from aviation, other air pollutants, noise and indicators for neighbourhood SES (n=287,167).

	Other air pollutants[1]					**Noise[1]**				**Neighbourhood SES[2]**					
	PM2.5	NO_2	EC	PM2.5- EC		Aviation (Schiphol)	Road traffic	Rail traffic		High edu.	Low edu.	Income	Unem-ployment	Social assistance	%non-western
UFP-aviation[1]	-0.09	0.00	-0.04	-0.10		0.43	-0.23	0.06		0.01	.,00	0.06	-0.03	-0.04	0.08
PM2.5	1.00	0.78	0.85	1.00		-0.12	0.12	0.11		0.03	0.04	0.05	0.00	0.14	0.04
NO_2		1.00	0.91	0.75		-0.13	0.28	0.31		0.26	-0.12	0.08	0.13	0.30	0.25
EC			1.00	0.81		-0.15	0.23	0.25		0.19	-0.08	0.07	0.08	0,24	0.19
PM2.5-EC				1.00		-0.12	0.10	0.09		0.00	0.05	0.05	-0.01	0.12	0.02
Aviation noise						1.00	-0.32	-0.08		-0.24	0.16	-0.08	-0.13	-0.08	0.06
Rail traffic noise							1.00	0.17		0.35	-0.25	0.08	0.17	0.18	0.13
Road traffic noise								1.00		0.19	-0.11	0.02	0.13	0.19	0.16
%High Education										1.00	-0.90	0.71	-0.10	-0.24	-0.16
%Low education											1.00	-0.80	0.20	0.47	0.36
Mean income												1.00	-0.30	-0.65	-0.59
Unemployment rate													1.00	0.58	0.47
Social assistance														1.00	0.83
%non-western															1.00

[1] During pregnancy.
[2] At the address of birth.

Table 4.5 Distribution of UFP from aviation during pregnancy stratified by degree of urbanization at neighbourhood level (UFP in #/cm³; other air pollutants in µg/m³).

	n	Mean	sd	p5	p10	p25	p50	p75	p90	p95	p99
UFP aviation											
1 (>2,500 addresses/km²)	156,371	1,841	956	744	888	1,203	1,621	2,219	3,009	3,810	5,291
2 (1,500-2,500 addresses/km²)	70,756	1,853	1,267	711	801	1,039	1,436	2,173	3,629	4,556	6,569
3 (1,000-1,500 addresses/km²)	32,957	1,983	1,297	803	91	1,156	1,521	2,450	3,536	4,301	7,426
4 (500-1,000 addresses/km²)	17,996	1,857	1,192	825	924	1,117	1,449	2,105	3,599	4,379	6,149
5 (<500 addresses/km²)	9,087	1,693	1,083	769	854	1,054	1,405	1,942	2,794	3,647	6,166
PM2.5											
1 (>2,500 addresses/km²)	156,371	15.4	2.9	11.2	11.9	13.1	15.0	17.7	19.7	20.6	22.1
2 (1,500-2,500 addresses/km²)	70,756	14.3	2.7	10.5	11.0	12.2	13.8	16.5	18.2	19.0	20.1
3 (1,000-1,500 addresses/km²)	32,957	14.5	2.6	10.5	11.1	12.3	14.4	16.7	18.1	18.7	19.6
4 (500-1,000 addresses/km²)	17,996	14.5	2.7	10.4	11.0	12.2	14.4	16.8	18.2	18.8	19.8
5 (<500 addresses/km²)	9,087	14.4	2.8	10.3	10.9	12.1	14.2	16.8	18.3	18.9	20.0
NO_2											
1 (>2,500 addresses/km²)	156,371	29.6	5.1	21.5	23.1	26.0	29.4	33.0	36.2	38.3	41.9
2 (1,500-2,500 addresses/km²)	70,756	25.4	4.6	18.0	19.5	22.2	25.2	28.5	31.5	33.3	36.8
3 (1,000-1,500 addresses/km²)	32,957	24.8	4.2	17.8	19.4	21.9	24.8	27.6	30.1	31.8	35.2
4 (500-1,000 addresses/km²)	17,996	24.8	4.5	17.3	18.8	21.7	24.9	27.9	30.5	32.1	35.5
5 (<500 addresses/km²)	9,087	24.0	4.8	16.3	17.9	20.6	23.8	27.1	30.1	32.2	36.8
EC											
1 (>2,500 addresses/km²)	156,371	1.3	0.4	0.8	0.8	1.0	1.2	1.5	1.8	2.0	2.3
2 (1,500-2,500 addresses/km²)	70,756	1.0	0.3	0.6	0.7	0.8	1.0	1.2	1.4	1.6	1.8
3 (1,000-1,500 addresses/km²)	32,957	1.0	0.3	0.6	0.7	0.8	1.0	1.2	1.4	1.5	1.8
4 (500-1,000 addresses/km²)	17,996	1.0	0.3	0.6	0.7	0.8	1.0	1.2	1.4	1.5	1.8
5 (<500 addresses/km²)	9,087	1.0	0.3	0.6	0.6	0.7	0.9	1.2	1.4	1.5	1.9

4.3.4 Correlation between different exposure metrics for UFP from aviation

Table 4.6 presents Spearman correlation coefficients between the different exposure metrics for UFP from aviation. UFP during pregnancy was highly correlated with UFP from aviation during each individual trimester of pregnancy (R 0.87-0.90). Correlations between the different trimesters were somewhat lower (R 0.61-0.70).

UFP from aviation during the second month of pregnancy (used as the main exposure metric in the analyses of congenital anomalies) was highly correlated with exposure during the first trimester (R = 0.8); correlations with the other exposure metrics were lower (ranging from 0.46 for exposure during the 3rd trimester to 0.68 for exposure during pregnancy).

Table 4.6 Spearman correlation between different UFP-aviation exposure metrics.

UFP-aviation	1st trim	2nd trim	3rd trim	3 months before	Total (~12 months	Peak exposure
Average during pregnancy	0.87	0.90	0.87	0.76	0.98	0.97
Average 1st trimester	1.00	0.70	0.61	0.70	0.87	0.85
Average 2nd trimester		1.00	0.70	0.62	0.87	0.87
Average 3rd trimester			1.00	0.67	0.86	0.84
3 months before pregnancy				1.00	0.87	0.95
Total period (~12 months)					1.00	0.74
Peak exposure						1.00

4.3.5 Associations between UFP from aviation and pregnancy outcomes

4.3.5.1 Main Model

4.3.5.1.1 *Primary outcomes*

Associations between UFP exposure at the residential address during pregnancy and pregnancy outcomes were, except for low birth weight, generally positive but did not reach statistical significance in the main model (Table 4.7). The association between UFP exposure and low birth weight was significantly negative when only gestational age, sex of the baby and parity was taken into account, but this significant association disappeared after adjusting for the maternal specific covariates and area level SES in model 2 and 3. The OR's varied between 0.95 (low birth weight) and 1.04 (extreme premature). When we modelled gestational age as continuous outcome variable, an increase in 3,500#/cm^3 of UFP from aviation was associated with a reduction in gestational length by 0.21 days (~5 hours; p=0.004). We found no association with a decrease in birth weight as continuous outcome.

4.3.5.1.2 *Secondary pregnancy outcomes*

We observed no statistically significant associations between UFP exposure during pregnancy and childhood mortality before age 1. Mortality between day 28 and 1 year (postnatal mortality) and UFP-exposure was positive, but this association was only based on 85 cases and not statistically significant. Associations between UFP-exposure and

congenital anomalies showed a positive trend, with OR's varying between 1.04 for anomalies of the circulatory system and 1.15 and 1.20 for anomalies of the nervous and senses system and the respiratory tract, respectively, but these associations did not reach statistical significance.

Association between exposure to UFP from aviation and Apgar were negative; compared to the reference group OR's were 0.85 (95%CI 0.75, 0.97) for a low Apgar score and 0.91 (95%CI 0.86-0.97) for an intermediate Apgar score (7 or 8).

Table 4.7 Associations between exposure to UFP from aviation and pregnancy outcomes.

	OR (95% CI)		
Health outcome	**Model 1**	**Model 2**	**Model 3**
Primary			
SGA	1.016 (0.977, 1.057)	1.028 (0.987, 1.07)	1.022 (0.981, 1.065)
Low BW (term)	**0.898 (0.811, 0.995)**	0.946 (0.854, 1.048)	0.947 (0.853, 1.051)
Preterm (GA <37w)	1.022 (0.969, 1.078)	1.047 (0.992, 1.105)	1.017 (0.963, 1.074)
Extr prem (GA <30w)	1.048 (0.881, 1.247)	1.072 (0.901, 1.275)	1.04 (0.871, 1.243)
Mod prem (GA 30-37w)	1.020 (0.965, 1.078)	1.045 (0.988, 1.105)	1.015 (0.959, 1.075)
Secondary			
Infant mortality (1st yr)	1.114 (0.974, 1.273)	0.991 (0.834, 1.178)	0.995 (0.835, 1.187)
Postnatal mortality: day28- 1 year[1]	1.534 (0.839, 2.804)	1.566 (0.842, 2.912)	1.435 (0.749, 2.747)
Ca-Any	1.072 (0.999, 1.150)	1.052 (0.98, 1.130)	1.054 (0.979, 1.134)
CA-Nervous & senses system	1.206 (0.995, 1.463)	1.157 (0.949, 1.411)	1.153 (0.94, 1.414)
CA- Circulatory system	1.064 (0.921, 1.229)	1.038 (0.897, 1.202)	1.04 (0.897, 1.207)
CA-Tractus digestivus	1.058 (0.878, 1.276)	1.055 (0.873, 1.274)	1.072 (0.885, 1.298)
CA-Tractus respiratorius	1.155 (0.853, 1.564)	1.145 (0.843, 1.556)	1.204 (0.88, 1.649)
CA-Tractus urogenitalus	1.131 (0.989, 1.295)	1.099 (0.958, 1.262)	1.107 (0.962, 1.274)
CA-Skin and abdominal wall	1.063 (0.873, 1.295)	1.046 (0.857, 1.277)	1.052 (0.857, 1.292)
CA-Muscolo-skeletal system	1.132 (0.976, 1.313)	1.123 (0.967, 1.304)	1.102 (0.947, 1.283)
Apgar (ordinal)	**0.899 (0.85, 0.95)**	**0.905 (0.856, 0.957)**	**0.896 (0.846, 0.949)**
Apgar <7	**0.859 (0.759, 0.973)**	**0.861 (0.76, 0.976)**	**0.851 (0.748, 0.967)**
Apgar 7, 8,	**0.908 (0.854, 0.965)**	**0.915 (0.86, 0.973)**	**0.906 (0.851, 0.966)**
Apgar 9, 10 (ref)	1	1	1

Odds Ratios (95% confidence intervals) presented for the 3,500#/cm^3 increase in UFP. Model 1 includes sex of the baby, parity and gestational age (for low birth weight and infant mortality; model 2 was further adjusted for maternal household income, maternal educational level, maternal marital status, maternal age at delivery and maternal region of origin; model 3 also includes percentage inhabitants with high education at area level and percentage inhabitants with a non-Western origin at area-level.

4.3.5.2 Further analyses primary outcomes

4.3.5.2.1 Splines

Figure 4.1 presents the shape of the exposure response curve for SGA, low birth weight, and preterm birth.

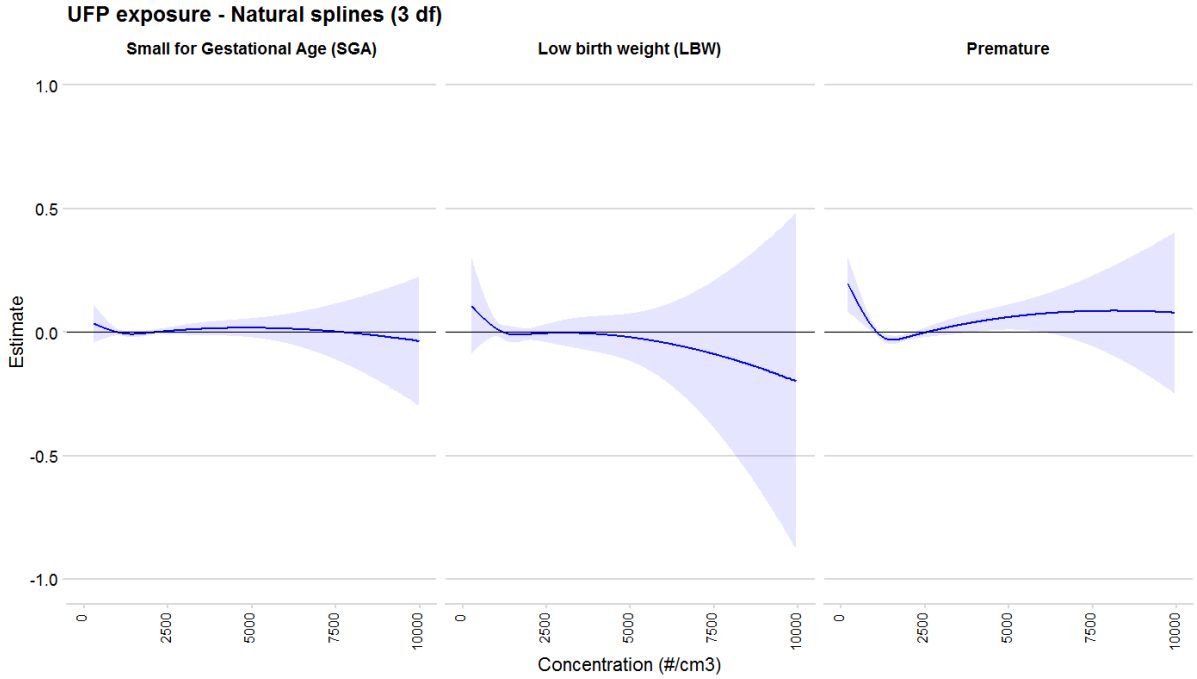


Figure 4.1 Natural cubic splines (3 df) for associations between UFP from aviation and SGA, prematurity and LBW (presentation limited to 10,000 #/cm3; full concentration range shown in appendix 4; figure A4.1).

We observed a decreasing trend at the lowest concentrations, especially for prematurity. This pattern is reversed for LBW and SGA and reduced when we excluded the 4 municipalities with the lowest UFP exposure (see appendix; figure A4.2); Also, for prematurity a significant increase between 4,000 and 6,000 #/cm^3 is visible in this analysis.

4.3.5.2.2 Exposure specification and adjustment for other air pollutants and noise

Results (main model) were similar for the other time-windows and peak exposures (figure 4.2), and after adjustment for other pollutants and noise (figure 4.3).

Adjustment for co-pollutants using a spline with 3 degrees of freedom (instead of a linear function) had no noteworthy impact on either the effect estimates or the concentration-response functions for LBW and SGA (results not shown). However, for prematurity, the effect estimate increased and became statistically significant at the $p<0.05$ level when adjusted for EC (OR 1.07 (95%CI 1.02, 1.13)) or NO_2 (OR 1.09 (95%CI 1.03, 1.15)) in this analysis. Spline plots for UFP from aviation and EC for different combinations of linear and non-parametric adjustment are included in the appendix (figures A4.3a&b). We chose EC, as non-linear adjustment for EC resulted in the strongest improvement of the fit (lowest AIC). Concentration-response curves for EC were highly non-linear (U-shaped), showing a significant decrease in prematurity with increasing EC for levels up to about 1 ug/m^3, and a significant increase for higher levels of EC, irrespective of (the type of) adjustment for UFP from aviation. Concentration-response curves for UFP from aviation were generally similar for different adjustments. However, a significant

increase in prematurity is observed between about 2,500 and 7,500 #/cm^3 with non-parametric adjustment for EC. Concentration-response curves for moderate prematurity were comparable (results not shown).

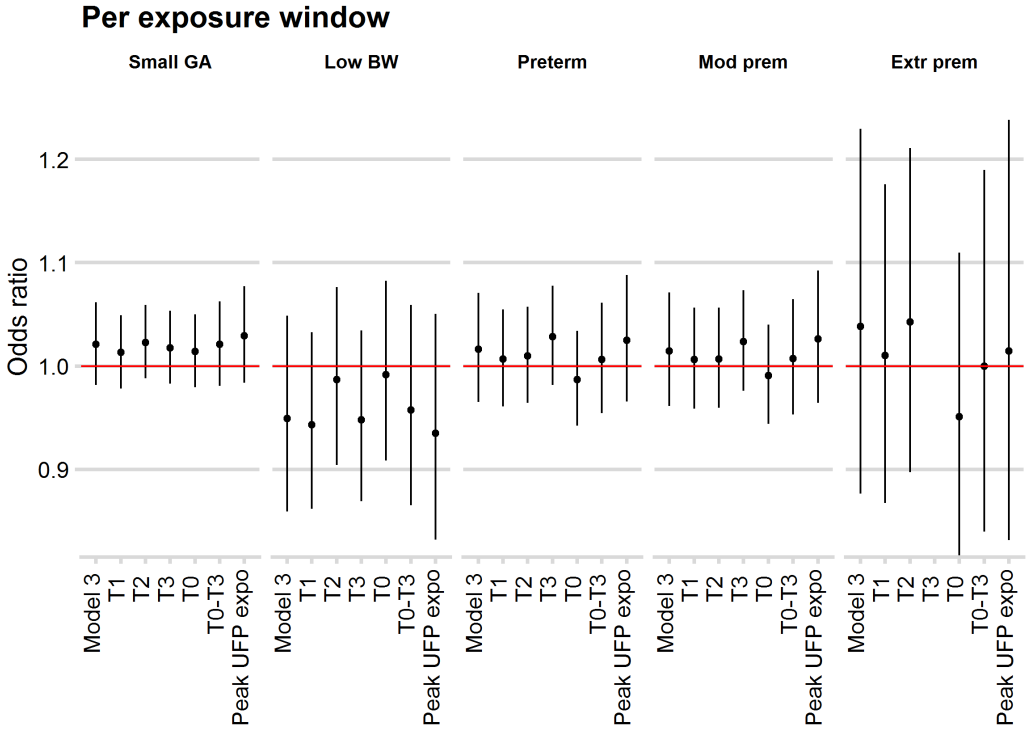


Figure 4.2 Associations between UFP from aviation and primary pregnancy outcomes at different exposure windows.
Odds Ratios (95% confidence intervals) presented for the 3,500#/cm^3 increase in UFP. Adjusted for sex of the baby, parity and gestational age (for low birth weight and infant mortality, maternal household income, maternal educational level, maternal marital status, maternal age at delivery and maternal region of origin, percentage inhabitants with high education and percentage inhabitants with a non-Western origin at neighbourhood level. Model 3: full pregnancy; T1: first trimester; T2: second trimester; T3: third trimester; T0: 3 months before pregnancy; Peak UFP: %hours > 66,667 #/cm3 during the full pregnancy, expressed per 100 hours/month. No effect estimate for T3 for extreme prematurity, as these children were born before the start of T3.

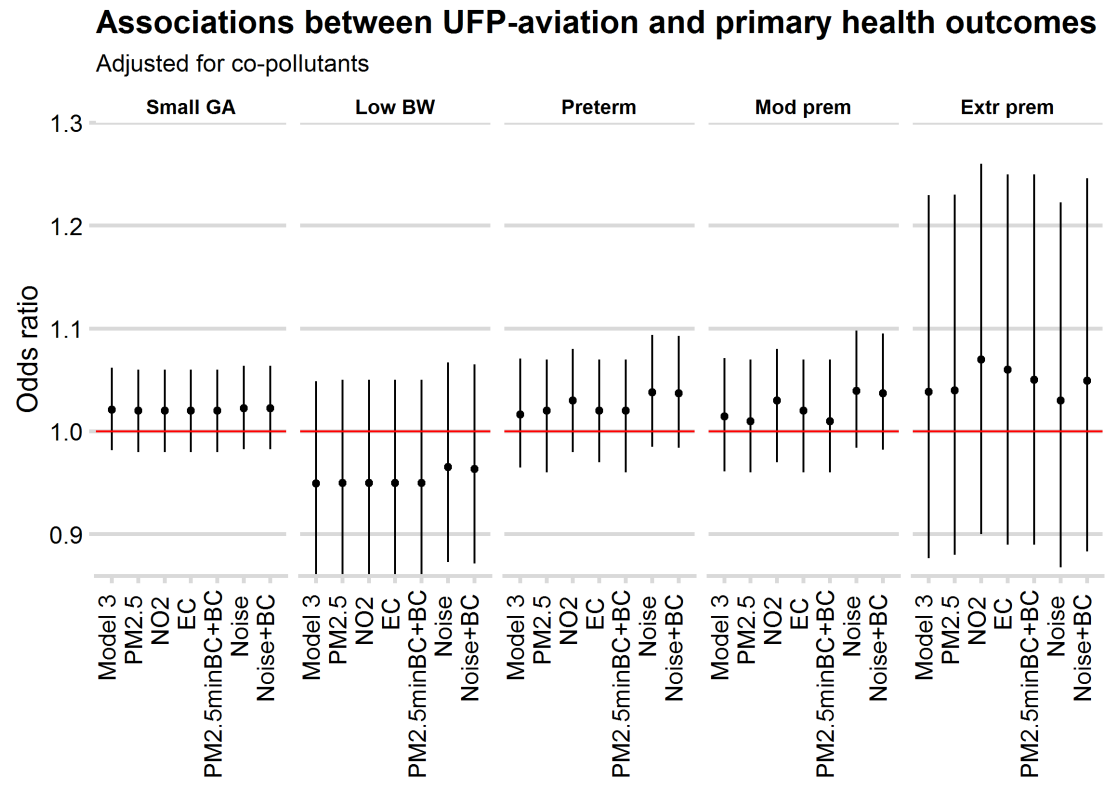


Figure 4.3 Associations between UFP from aviation and primary pregnancy outcomes in multi-exposure models. See figure 4.2 for model specification.

4.3.5.2.3 Sensitivity analyses and stratifications

Results were generally robust in the different sensitivity analyses (figure 4.4-4.7).

The main exception is the sensitivity analysis excluding the four municipalities with the lowest average UFP exposure, after which effect estimates increase for all primary outcomes and become (borderline) significant for SGA (OR 1.04 (95%CI 0.99-1.09); p=0.09), premature birth (OR 1.06 (95% CI 1.00-1.13); p=0.04) and moderate premature birth (OR 1.06 (95% CI 1.00-1.13); p=0.07). Effect estimates for (moderate) preterm birth also became borderline significant (p<0.10) when the population was restricted to mothers with a Dutch background (OR 1.07 (95% 1.00-1.16). Also (borderline) significant associations were found between UFP and preterm birth (OR 1.11 (95%CI 1.00-1.22); p=0.04) and extreme preterm birth (OR 1.30 (95%CI 0.99-1.69);p=0.06) in births with induced labour onset or planned caesarean section. In addition, we observe a borderline significant inverse association for LBW when mothers who lived in the municipality of Amsterdam at the date of either conception or birth were excluded (OR 0.88 (95% CI 0.77-1.01); p=0.06).

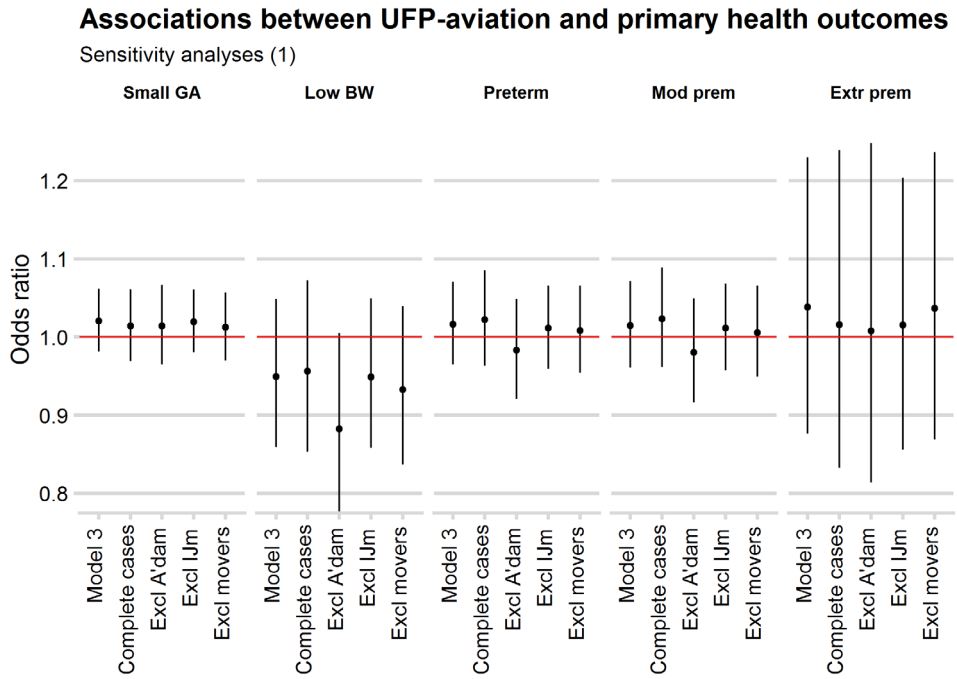


Figure 4.4 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (1). See figure 4.2 for model specification.

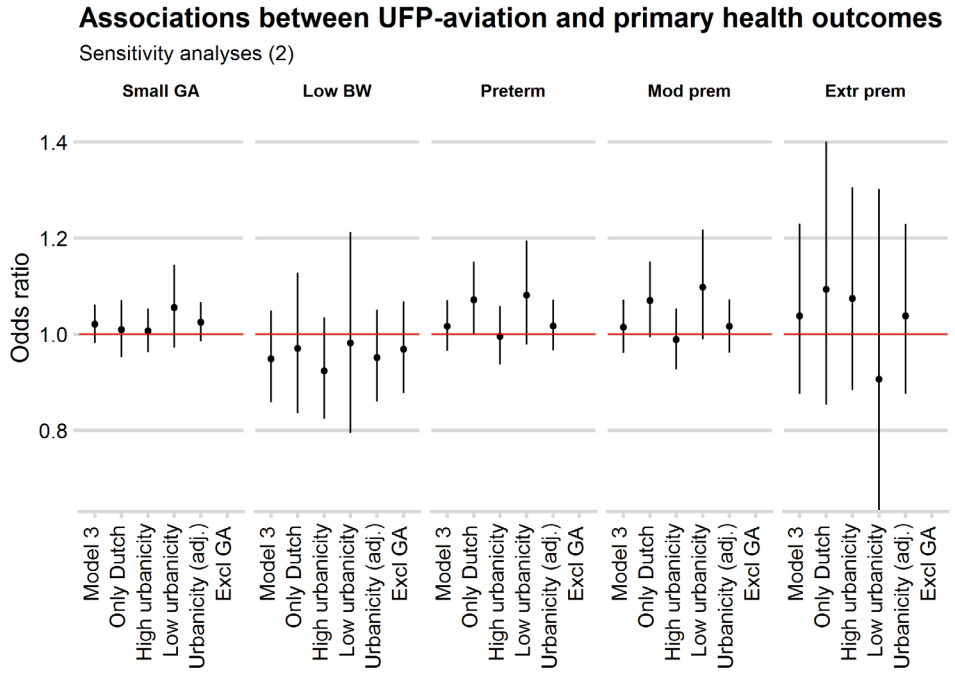


Figure 4.5 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (2). See figure 4.2 for model specification.

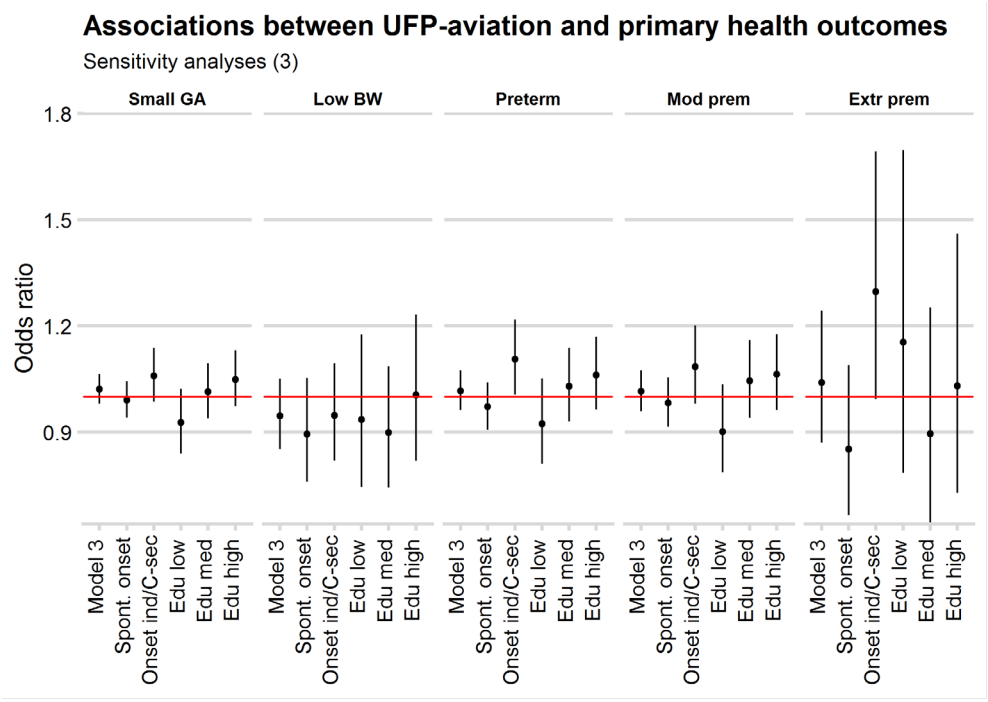


Figure 4.6 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (3). See figure 4.2 for model specification.

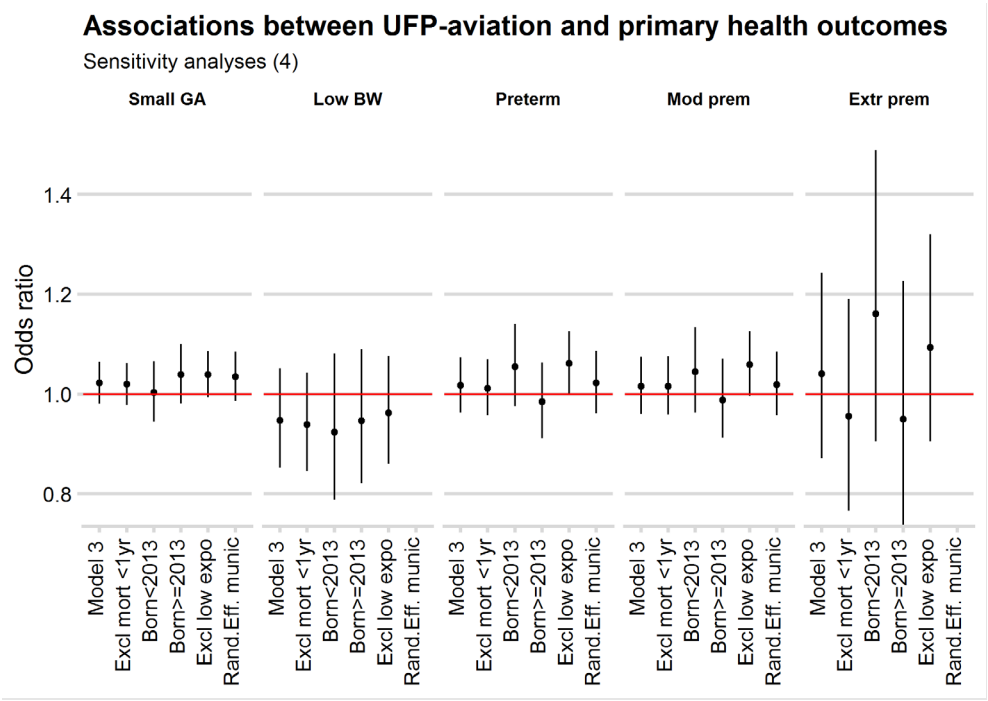


Figure 4.7 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (4). See figure 4.2 for model specification.

4.3.5.3 Further analyses secondary outcomes: infant mortality

4.3.5.3.1 Splines

Figure 4.8 presents the shape of the exposure response curve for infant mortality. We observed no strong deviations from normality; the increasing trend at low concentrations is reduced when the 4 municipalities with the lowest UFP exposure are excluded (see appendix; figure A4.4).

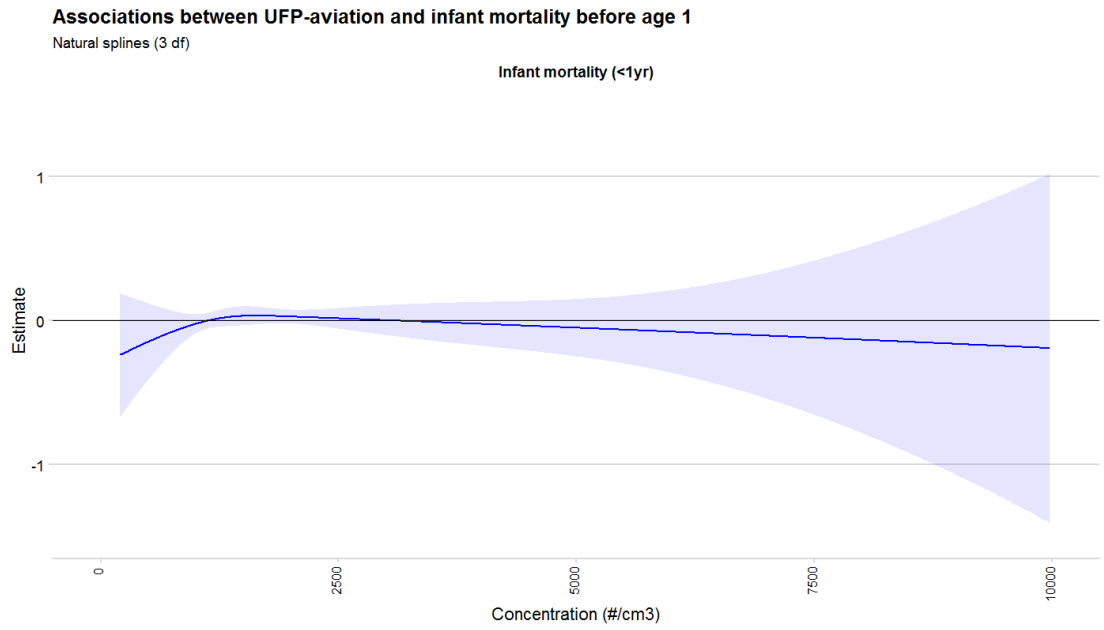


Figure 4.8 Natural cubic splines (3 df) for associations between UFP from aviation and infant mortality (presentation limited to 10,000 #/cm³).

Results (main model) were similar for the other time-windows and peak exposures (figure 4.9), after adjustment for other pollutants and noise, as well as in the different sensitivity analyses (figure 4.10).

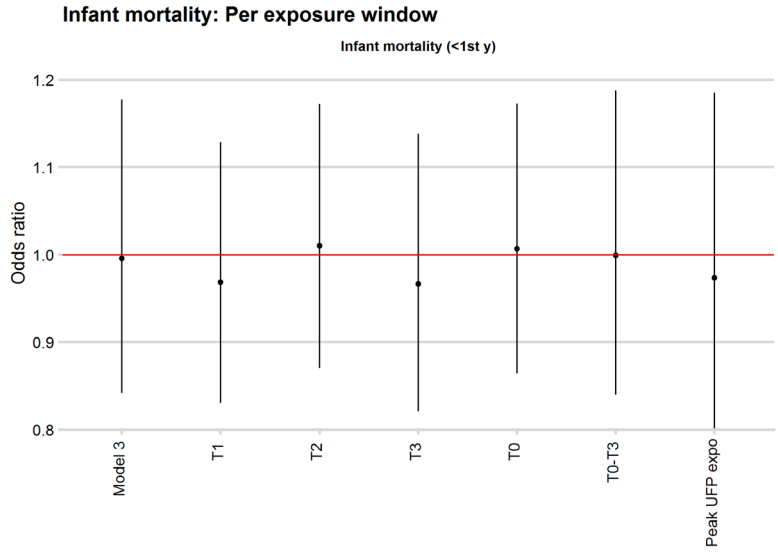
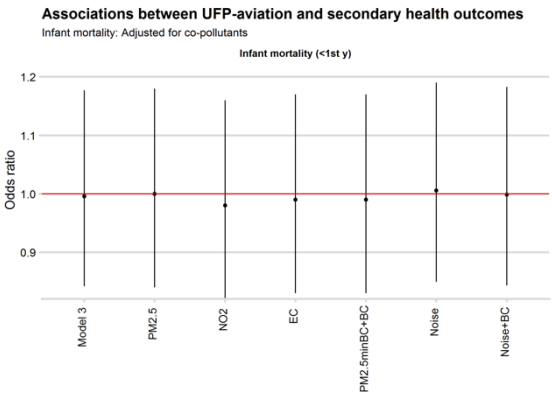
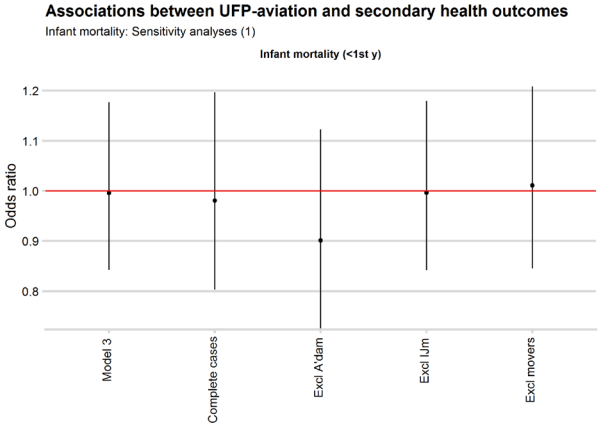
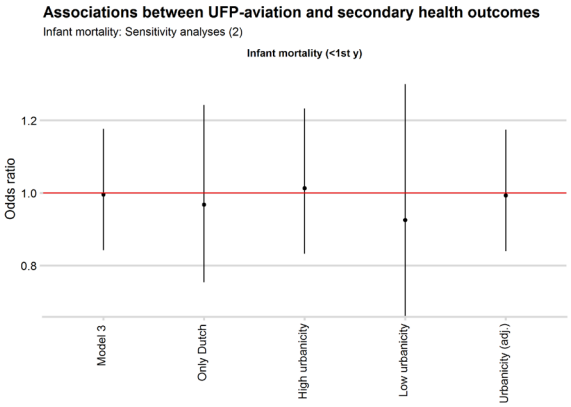
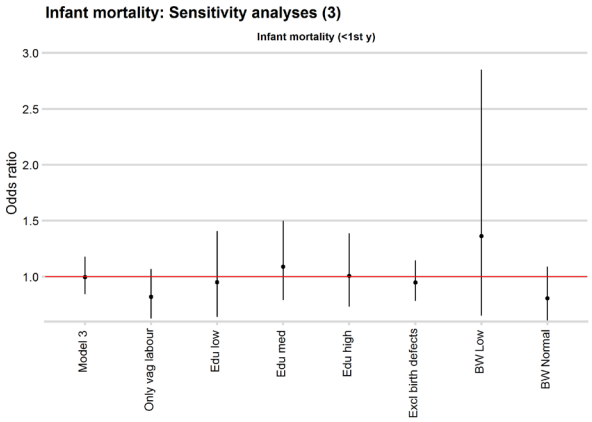


Figure 4.9 Associations between UFP from aviation and infant mortality for different exposure windows. See figure 4.2 for model specification.









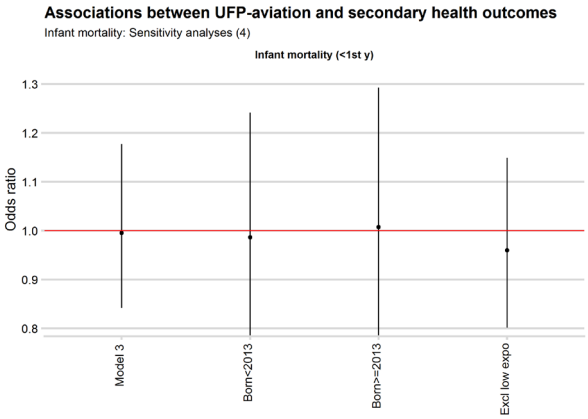


Figure 4.10 Associations between UFP from aviation and infant mortality in multi-exposure models and sensitivity analyses. See figure 4.2 for model specification.

4.3.5.4 Further analyses secondary outcomes: congenital anomalies

4.3.5.4.1 Splines

Figure 4.11 presents the shapes of the exposure response curve for congenital anomalies. Spline plots generally confirmed the results of the linear analyses. Anomalies of the digestive system and skin and abdominal wall showed a drop at the highest exposure range, however confidence intervals for the high exposed areas were wide as result of the few cases of these specific anomalies, i.e. <0.20% for the complete study population.

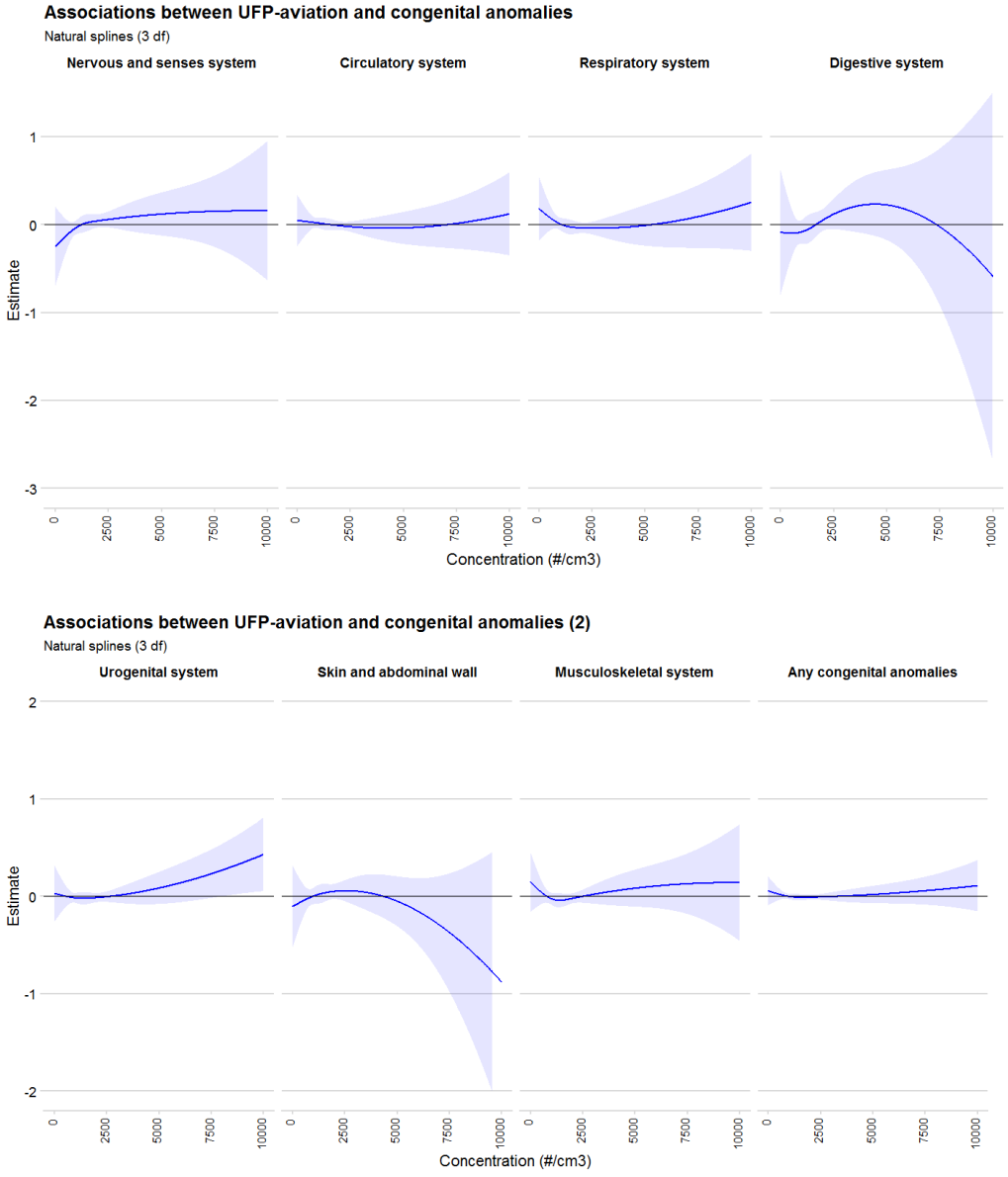


Figure 4.11 Natural cubic splines (3 df) for associations between UFP from aviation and congenital anomalies (presentation limited to 10,000 #/cm3).

4.3.5.4.2 Exposure specification and adjustment for other air pollutants and noise

Results for the different exposure windows and peak exposures are presented in figure 4.12 for congenital anomalies of the nervous and senses system, circulatory system, digestive system and respiratory

tract; and in figure 4.13 for congenital anomalies of the tractus urogenitalis, skin and abdominal wall, musculoskeletal system and any of these congenital anomalies reported. Associations were generally similar for the different exposure specifications. However, for congenital anomalies of the nervous & senses system, we observed a significant association with exposure to UFP from aviation during the 3 months before pregnancy (OR 1.29 (95%CI 1.02-1.63). To confirm that exposure during the second month of pregnancy is the most relevant exposure window, also exposure during the third trimester was included in the model (appendix A4.5). Results indicate that in general associations during the second month did not change, while associations with exposure during the third trimester attenuated. This indicates that exposure during the second month is most relevant.

Associations were insensitive to adjustment for other air pollutants and noise for all classes of congenital anomalies (figure 4.14 and 4.15).

4.3.5.4.3 Sensitivity analyses and stratifications

Results from the different sensitivity analyses generally did not show strong deviations from the results of the main model (figure 4.16 – 4.23), with the exception of the sensitivity analyses excluding the four municipalities with the lowest average UFP exposure and the random effect model. After excluding the four municipalities with the lowest average UFP exposure, effect estimates increase for all 7 types of anomalies, with the association becoming (borderline) significant for anomalies of the urogenital system (p=0.03), circulatory system (p=0.09) and musculoskeletal system (p=0.07). These are also the 3 categories of anomalies with the highest number of cases (n=1,119, 1,045 and 945, respectively). The OR for the combined variable 'any anomaly' increases from 1.05 to 1.11 and becomes significant at the p<0.01 level (95% CI 1.03-1.20; p=0.007). When 'municipality' was included as a random effect, effect estimates increased and became (borderline) significant for anomalies of the urogenital system (OR 1.16 (95%CI 1.00, 1.34)), skin and abdominal wall (OR 1.21 (95%CI 0.97, 1.50)), musculoskeletal system (OR 1.17 (95%CI 1.00, 1.38)) and 'any anomaly' (OR 1.14 (95%CI 1.05, 1.23)).

We also observed significant associations in some specific strata of the population, i.e. for anomalies in the circulatory system (OR 1.34 (95%CI 1.04, 1.67)), urogenital system (OR 1.41 (95%CI 1.10, 1.80)) and any anomaly (OR 1.18 (95%CI 1.02, 1.35)) for children born in low urbanized neighbourhoods; and for anomalies of the nervous & senses system (OR 1.47 (95%CI 1.07-2.02)) and respiratory system OR 1.74 (95%CI 1.03-2.92),) for births from mothers with a medium education level and for anomalies of the tractus urogenitalus (OR 1.31 (95%CI 1.05, 1.63)) and any congenital anomaly OR 1.14 (95%CI 1.01, 1.29)) for births from mothers with a high education level. When stratified by period of birth, the association was significant for anomalies of the nervous & senses system (OR 1.34 (95%CI 1.02, 1.76)) for children born before 2013 and for musculoskeletal system (OR 1.23 (95%CI 1.01, 1.49)) for children born from 2013 onwards.

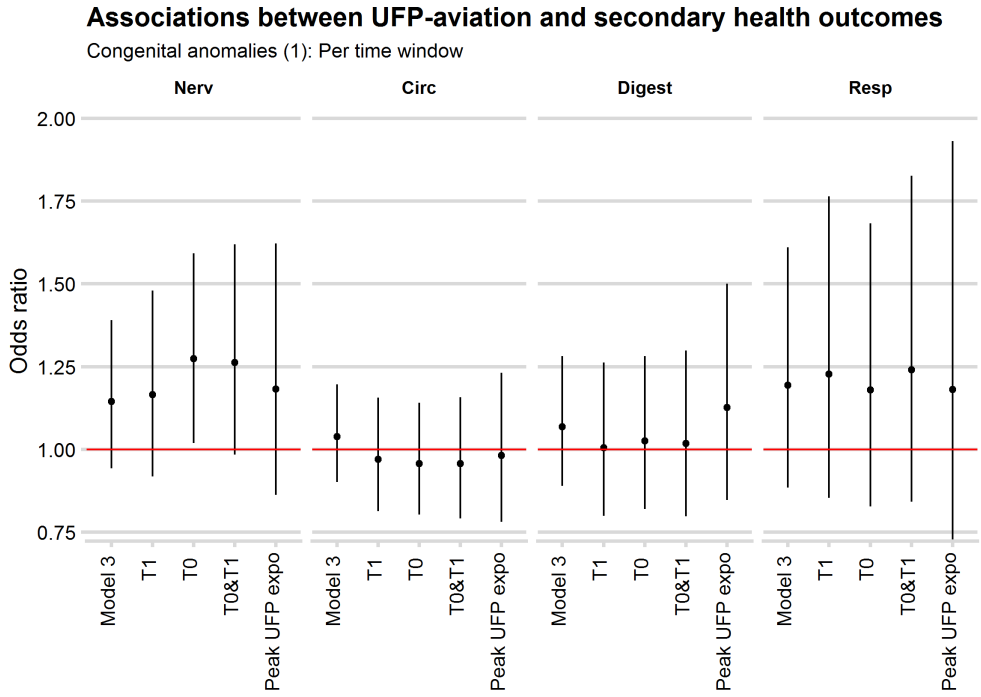


Figure 4.12 Associations between UFP from aviation and congenital anomalies of the nervous and senses system (Nerv), circulatory system (Circ), tractus digestivus (Digest) and tractus respiratorius (Resp) for different exposure specifications. See figure 4.2 for model specification.

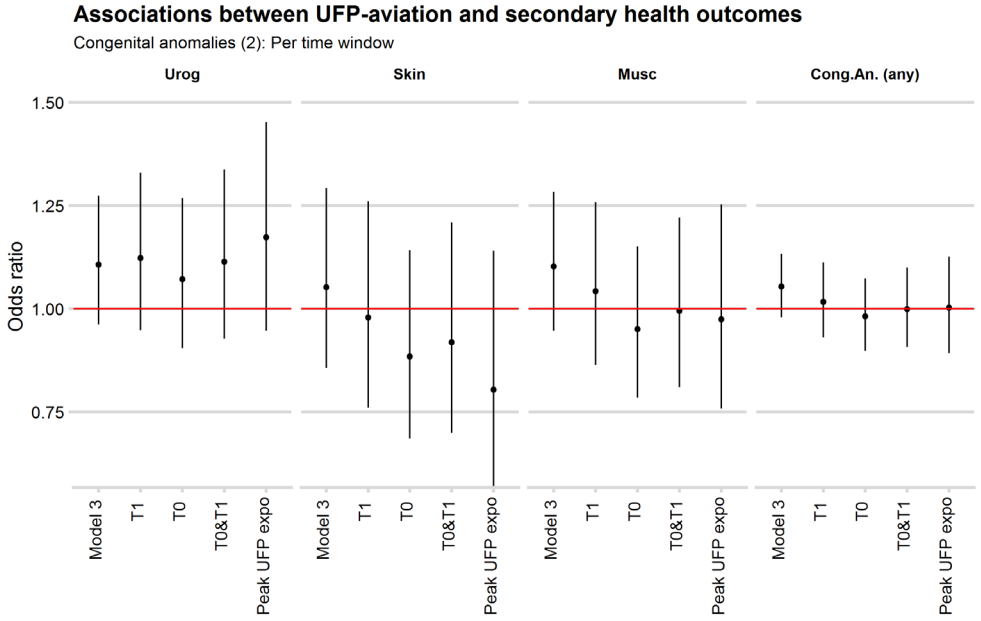


Figure 4.13 Associations between UFP from aviation and congenital anomalies of the tractus urogenitalus (Urog), skin and abdominal wall (Skin),musculoskeletal system (Musc) and any congenital anomaly for different exposure specifications. See figure 4.2 for model specification.

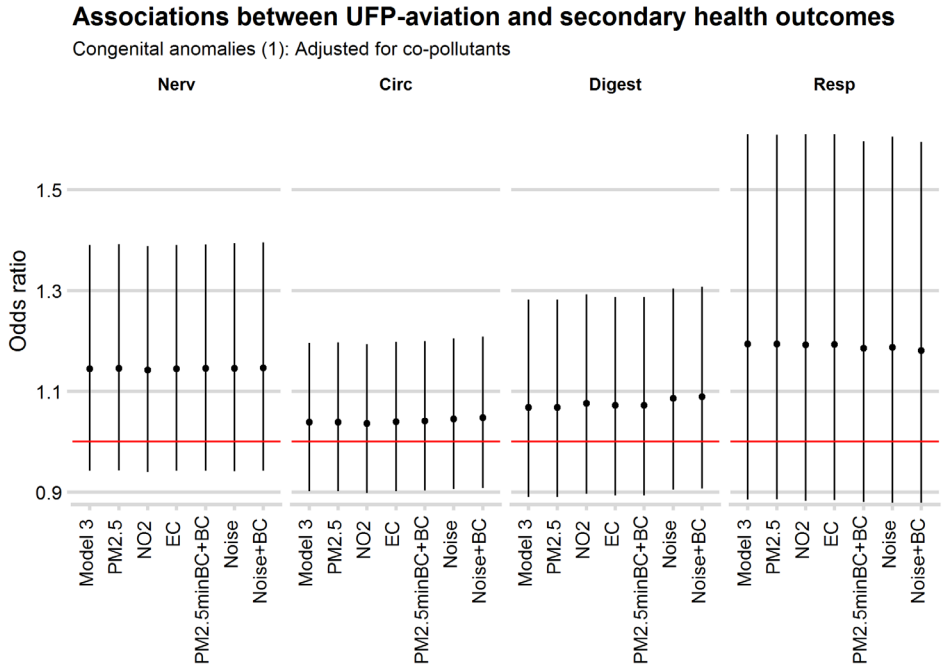


Figure 4.14 Associations between UFP from aviation and congenital anomalies of the nervous and senses system (Nerv), circulatory system (Circ), tractus digestivus (Digest) and tractus respiratorius (Resp) in multi-exposure models. See figure 4.2 for model specification.

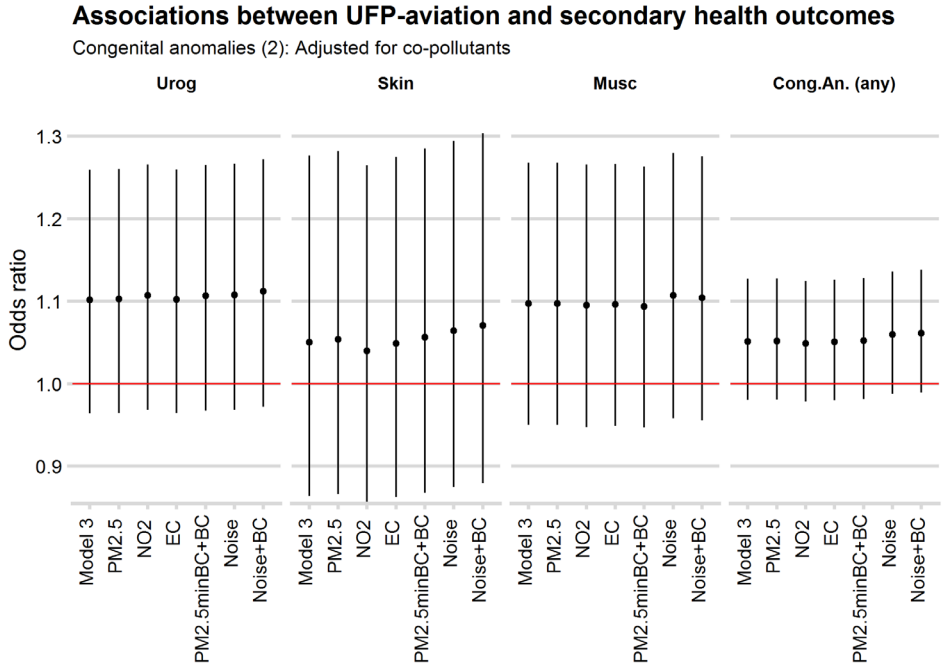


Figure 4.15 Associations between UFP from aviation and congenital anomalies of the tractus urogenitalus (Urog), skin and abdominal wall (Skin), musculoskeletal system (Musc) and any congenital anomaly in multi-exposure models. See figure 4.2 for model specification.

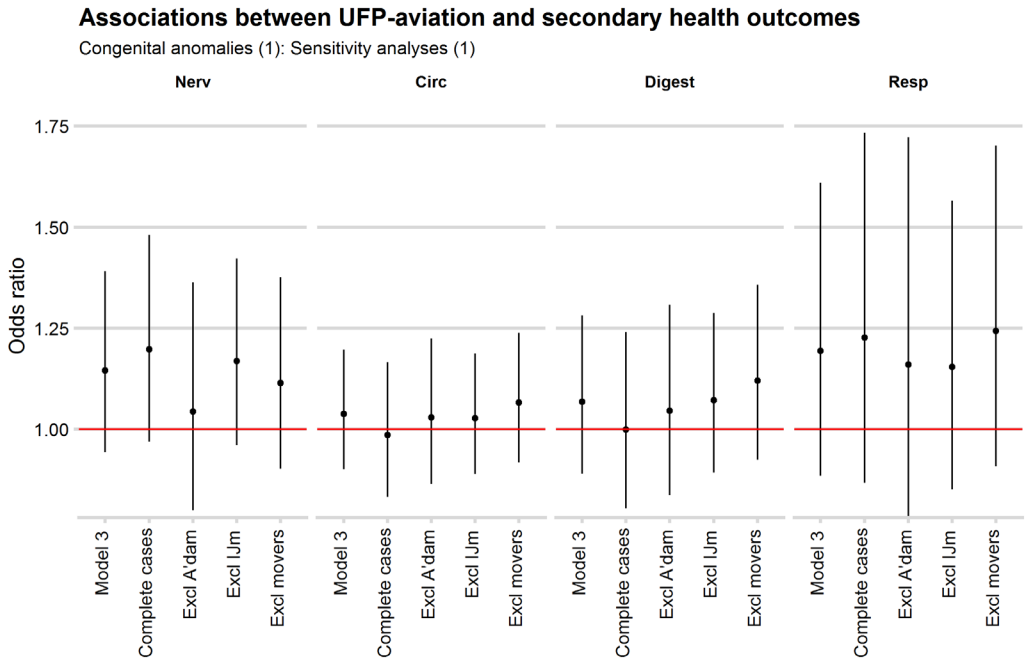


Figure 4.16 Associations between UFP from aviation and congenital anomalies of the nervous and senses system (Nerv), circulatory system (Circ), tractus digestivus (Digest) and tractus respiratorius (Resp) sensitivity analyses (1). See figure 4.2 for model specification.

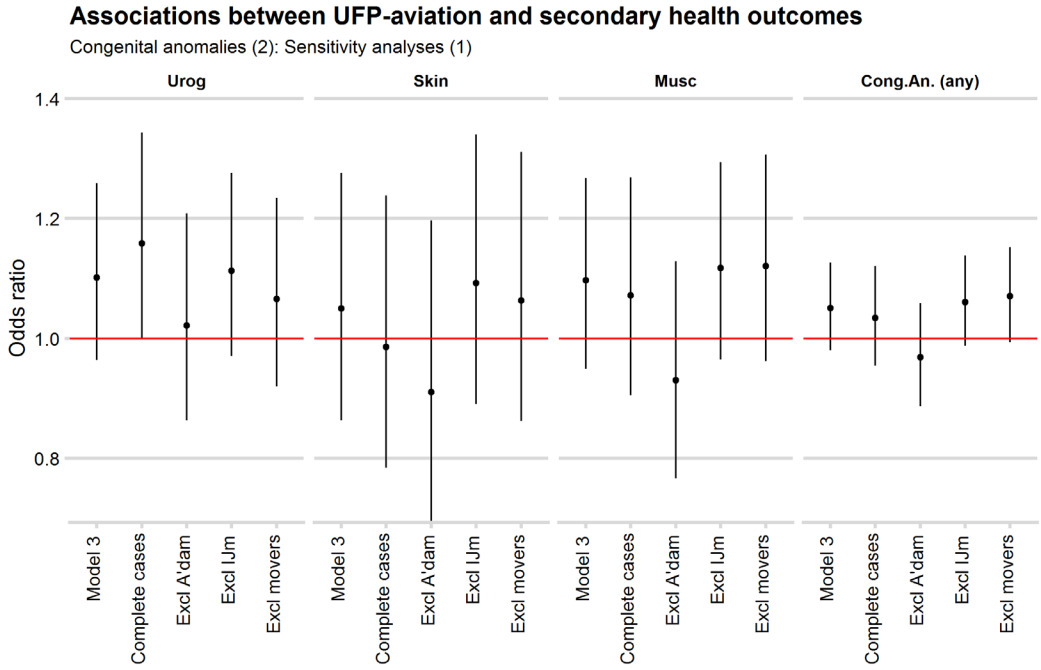


Figure 4.17 Associations between UFP from aviation and congenital anomalies of the tractus urogenitalus (Urog), skin and abdominal wall (Skin), musculoskeletal system (Musc) and any congenital anomaly (CA any) - sensitivity analyses (1). See figure 4.2 for model specification.

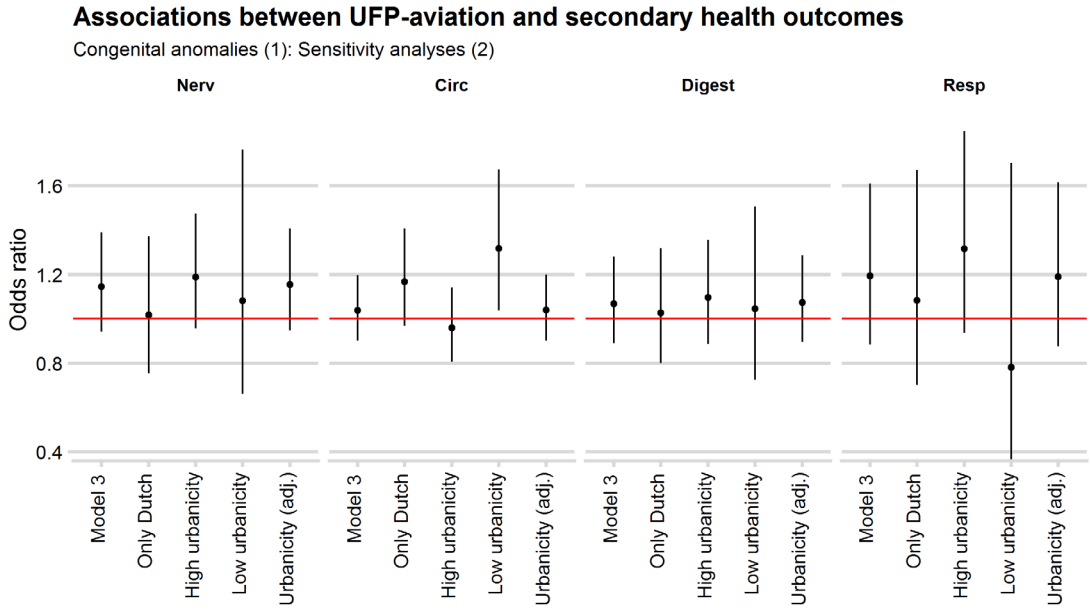


Figure 4.18 Associations between UFP from aviation and congenital anomalies of the nervous and senses system (Nerv), circulatory system (Circ), tractus digestivus (Digest) and tractus respiratorius (Resp) sensitivity analyses (2).

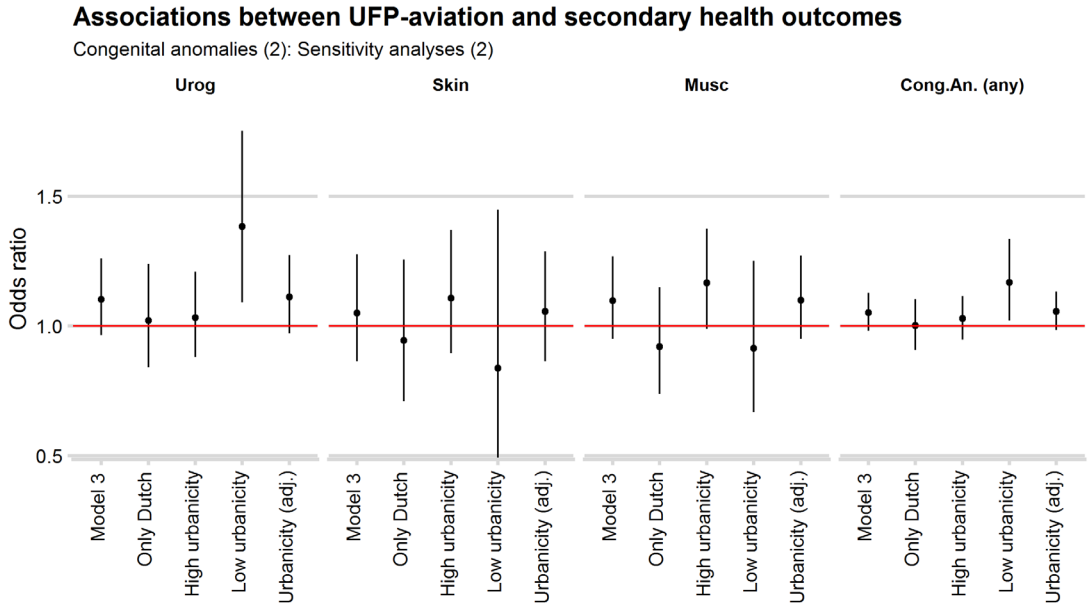


Figure 4.19 Associations between UFP from aviation and congenital anomalies of the tractus urogenitalus (Urog), skin and abdominal wall (Skin), musculoskeletal system (Musc) and any congenital anomaly (CA any) - sensitivity analyses (2). See figure 4.2 for model specification.

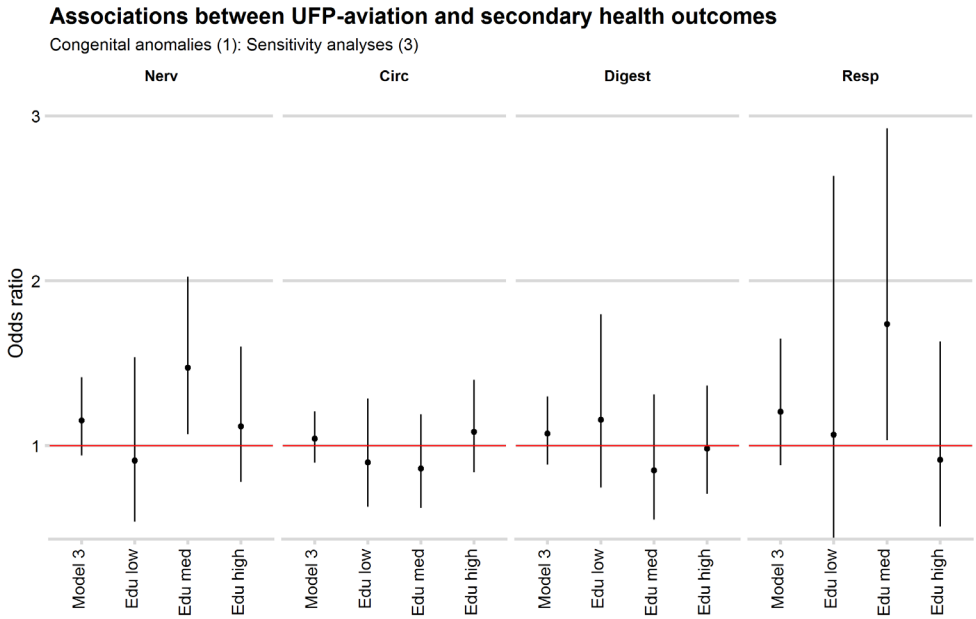


Figure 4.20 Associations between UFP from aviation and congenital anomalies of the nervous and senses system (Nerv), circulatory system (Circ), tractus digestivus (Digest) and tractus respiratorius (Resp) sensitivity analyses (3). See figure 4.2 for model specification.

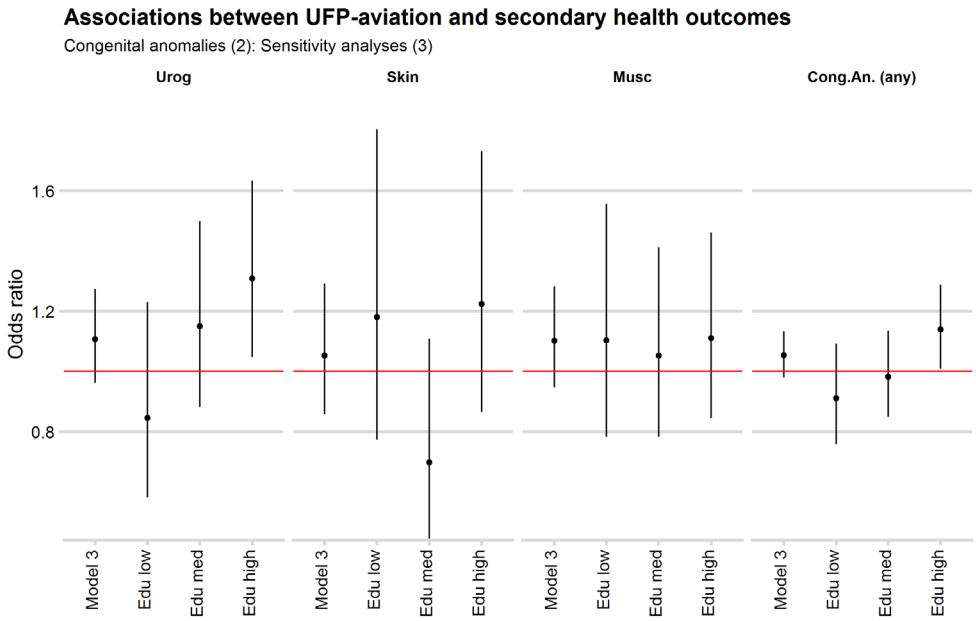


Figure 4.21 Associations between UFP from aviation and congenital anomalies of the tractus urogenitalus (Urog), skin and abdominal wall (Skin), musculoskeletal system (Musc) and any congenital anomaly (CA any) - sensitivity analyses (3). See figure 4.2 for model specification.

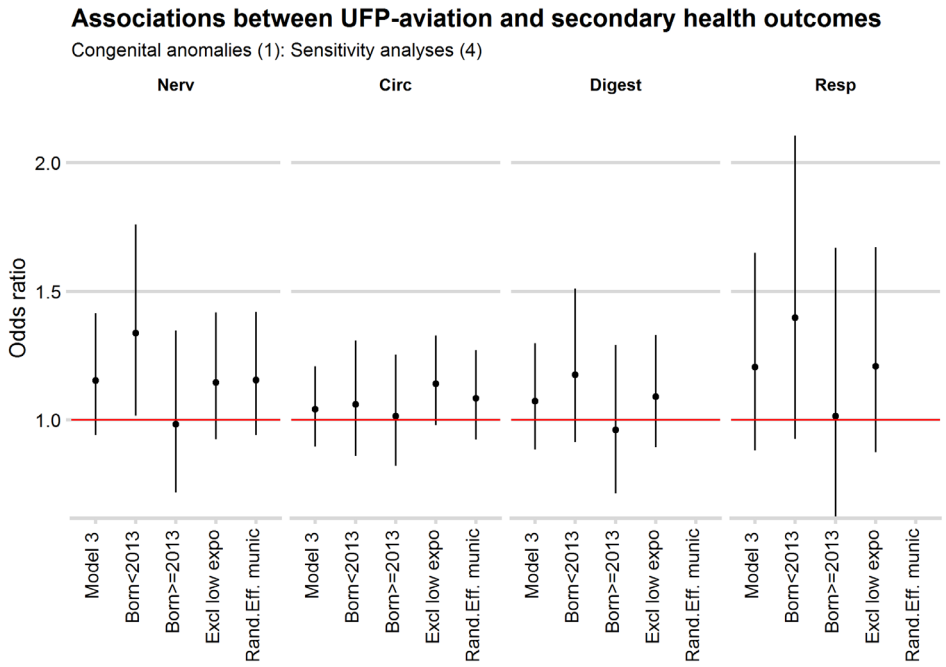


Figure 4.22 Associations between UFP from aviation and congenital anomalies of the nervous and senses system (Nerv), circulatory system (Circ), tractus digestivus (Digest) and tractus respiratorius (Resp) sensitivity analyses (4). See figure 4.2 for model specification.

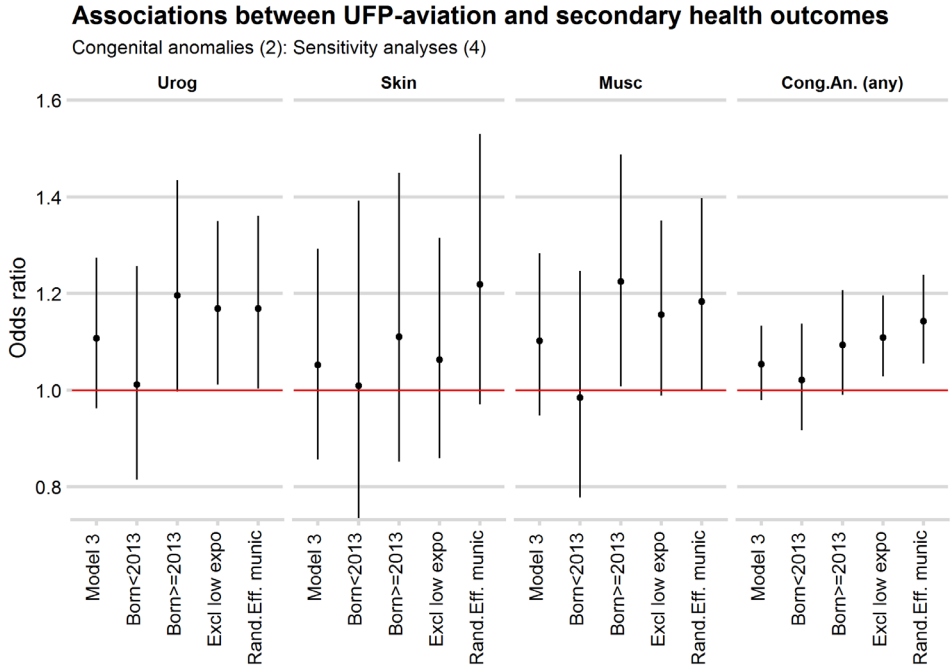


Figure 4.23 Associations between UFP from aviation and congenital anomalies of the tractus urogenitalus (Urog), skin and abdominal wall (Skin), musculoskeletal system (Musc) and any congenital anomaly (CA any) - sensitivity analyses (4). See figure 4.2 for model specification.

4.3.5.5 Further analyses secondary outcomes: Apgar score

4.3.5.5.1 Splines

Figure 4.24 presents the shape of the exposure response curve for Apgar scores. We observed a strong decrease at the lowest concentrations. This pattern is substantially reduced when the 4 municipalities with the lowest UFP exposure are excluded (see appendix; Figure A4.6);

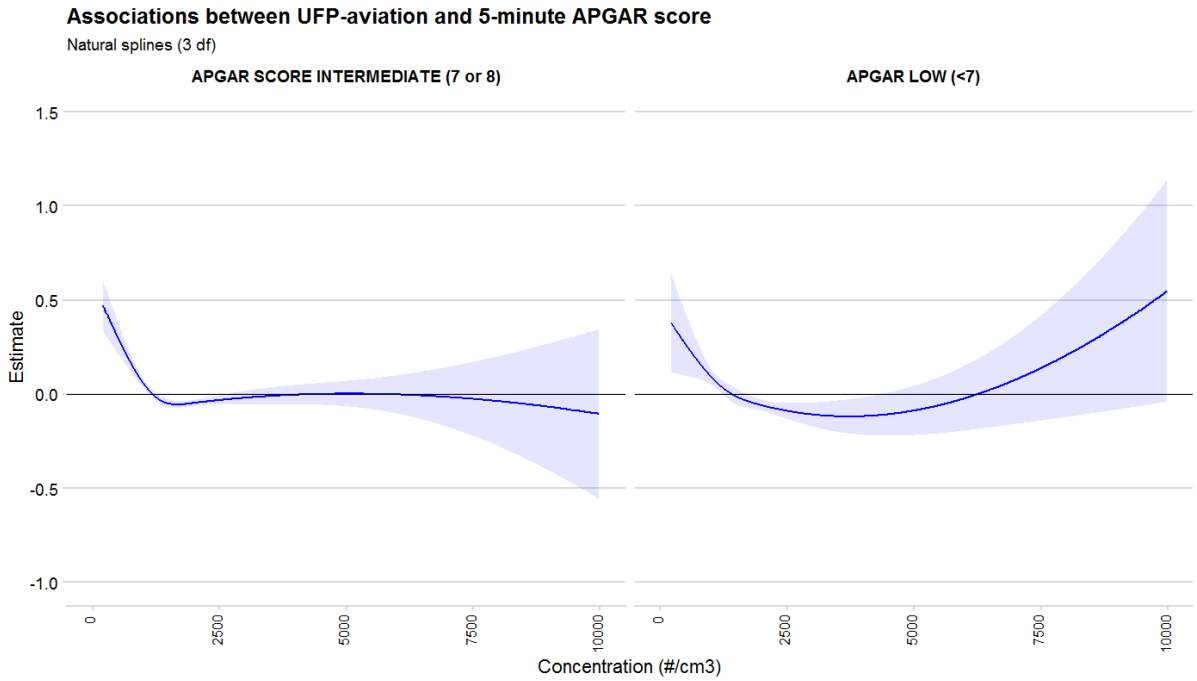


Figure 4.24 Natural cubic splines (3 df) for associations between UFP from aviation and Apgar scores (presentation limited to 10,000 #/cm3).

4.3.5.5.2 Exposure specification and adjustment for other air pollutants and noise

Results (main model) were similar for the other time-windows and peak exposures (figure 4.25), and after adjustment for other pollutants and noise (figure 4.26).

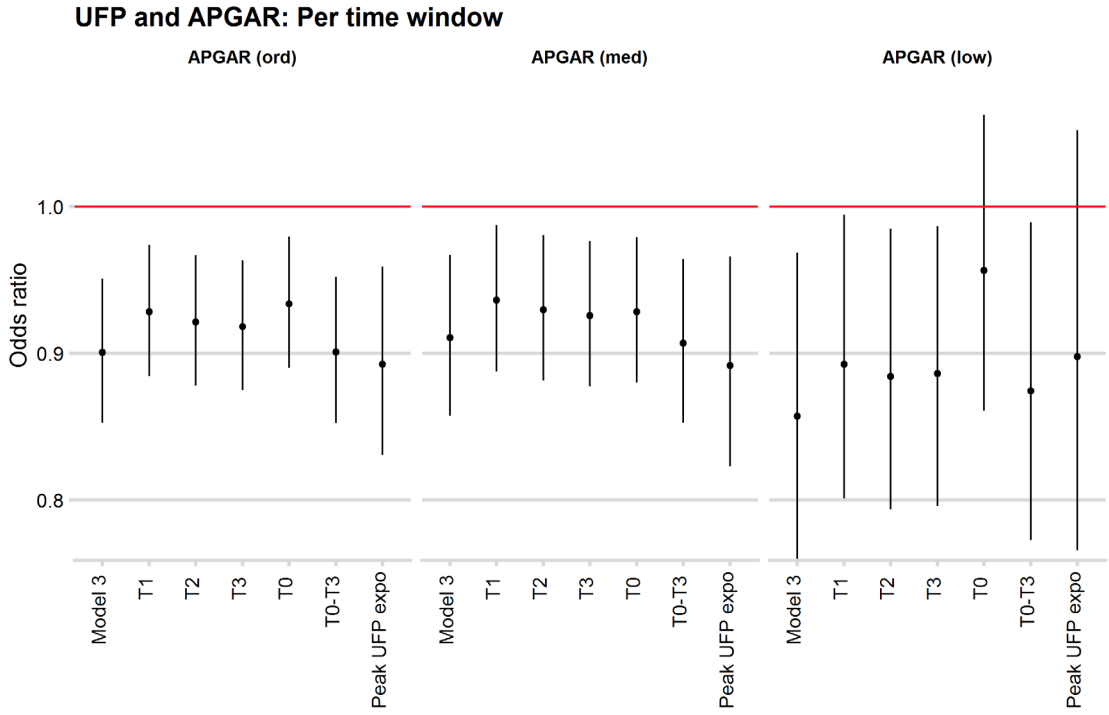


Figure 4.25 Associations between UFP from aviation and 5-minute Apgar score for different exposure windows. See figure 4.2 for model specification.

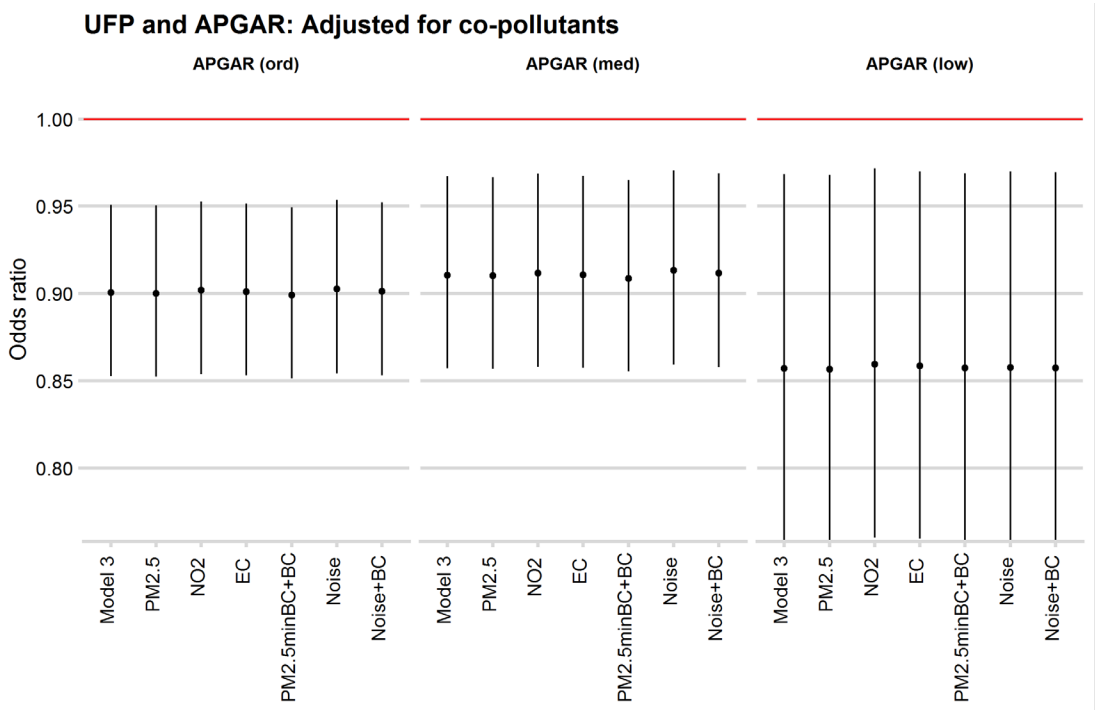


Figure 4.26 Associations between UFP from aviation and 5-minute Apgar score in multi-exposure models. See figure 4.2 for model specification.

4.3.5.5.3 Sensitivity analyses and stratifications

The inverse associations between UFP and Apgar scores persisted in all sensitivity analyses, with exception of exclusion of the four municipalities with the lowest average UFP exposure and the inclusion of 'municipality' as a random effect. In both analyses, effect estimates strongly attenuate and loose statistical significance; Furthermore, addition of the random effect for municipality substantially improved the model fit (result not shown).

Effect estimates are also non-significant for some specific strata of the population (e.g. children born in low urbanized neighbourhoods and children born after 2013).

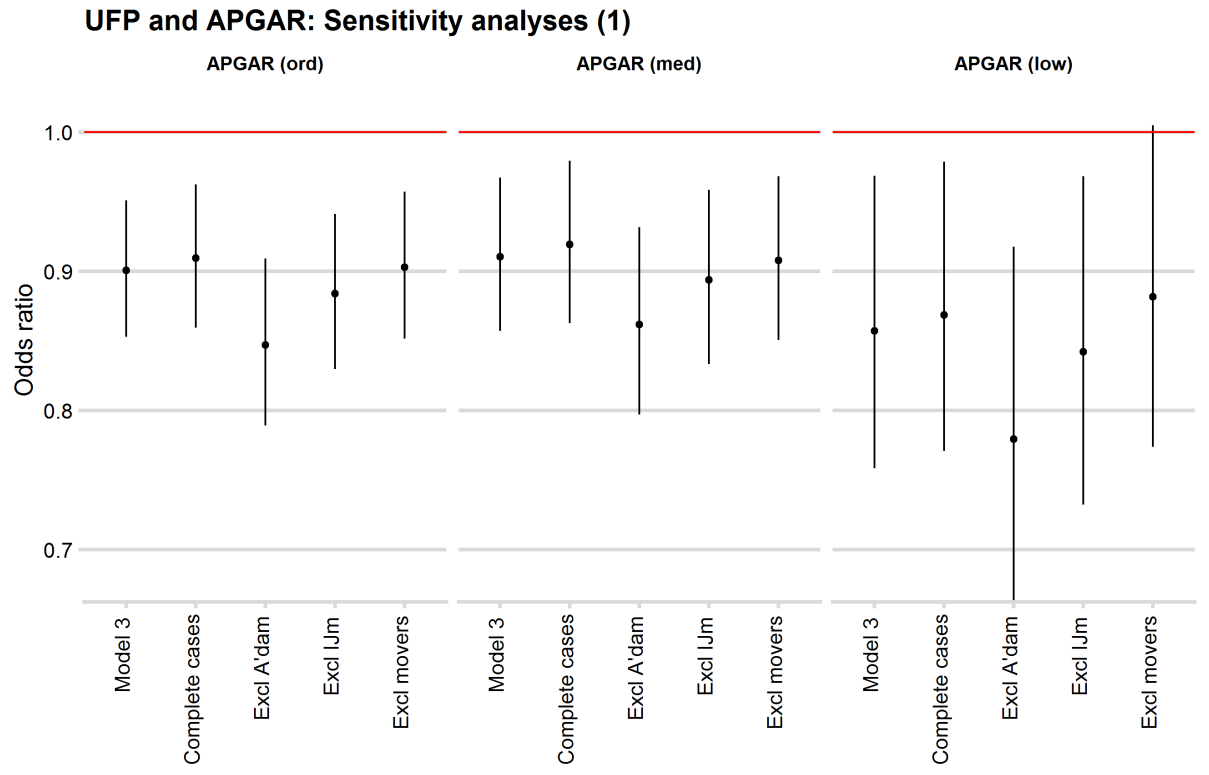


Figure 4.27 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (1). See figure 4.2 for model specification.

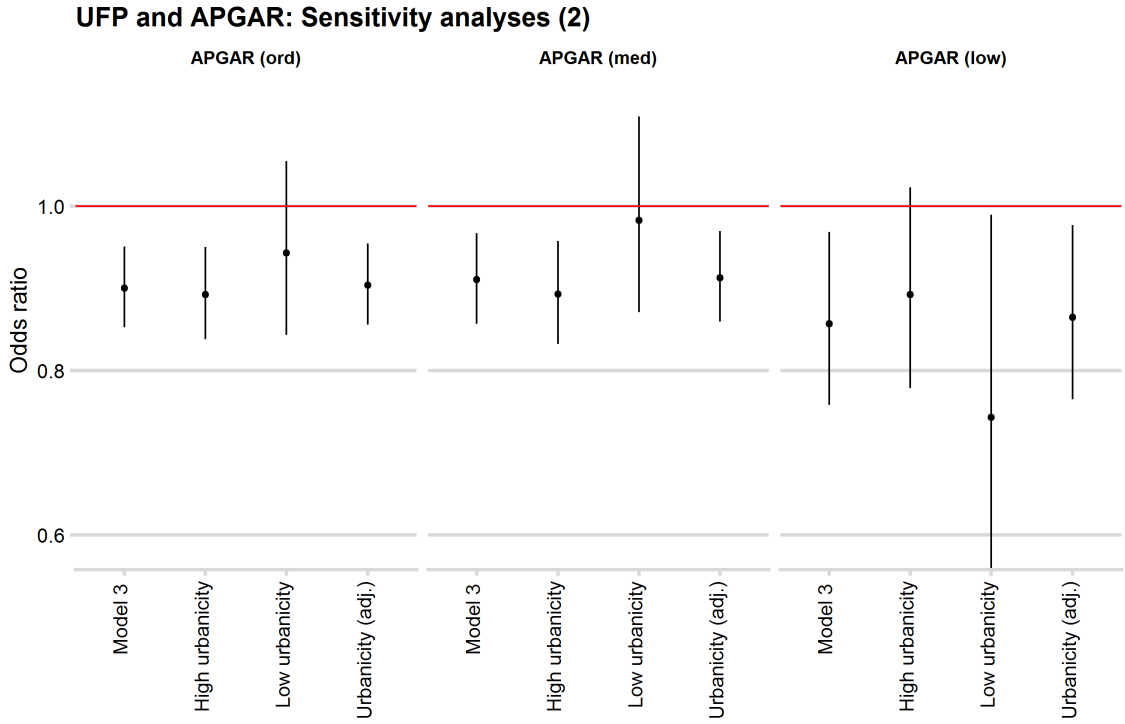


Figure 4.28 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (2). See figure 4.2 for model specification.

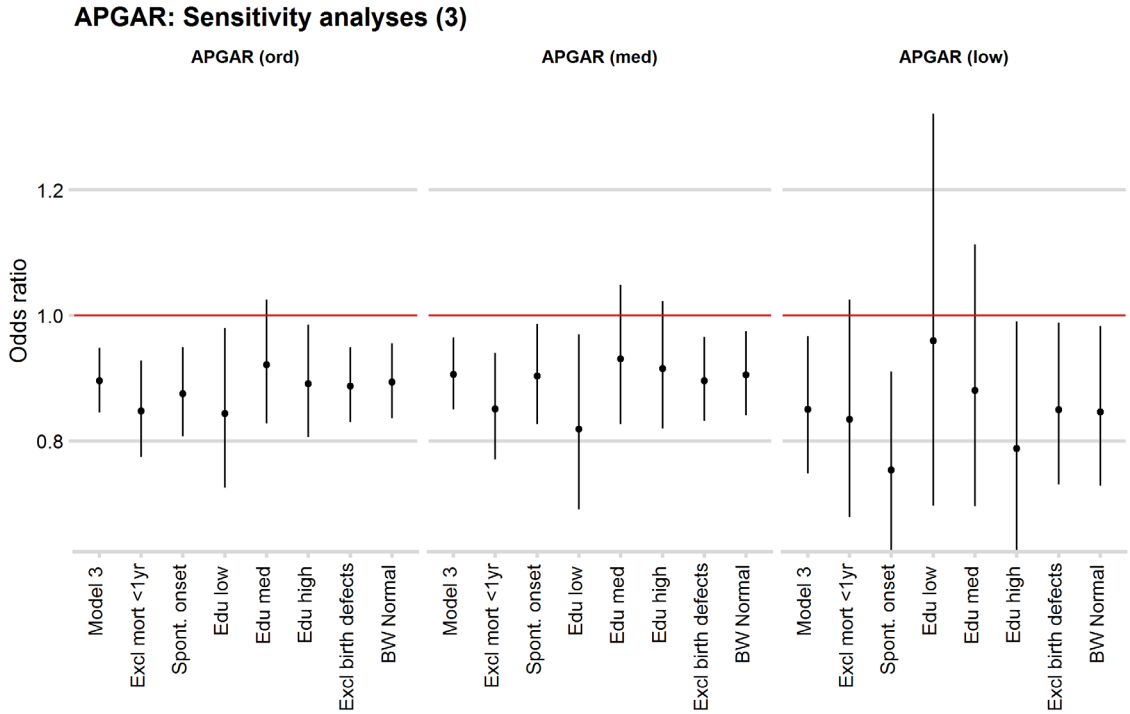


Figure 4.29 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (3). See figure 4.2 for model specification.

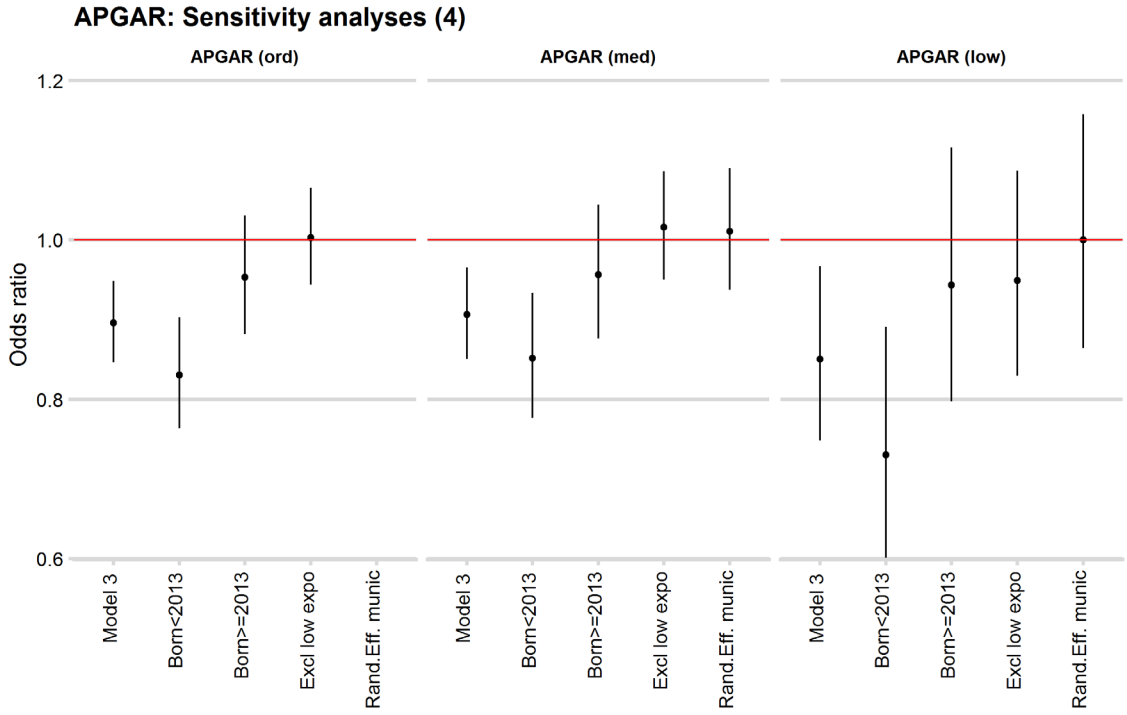


Figure 4.30 Associations between UFP from aviation and primary pregnancy outcomes – sensitivity analyses (4). See figure 4.2 for model specification.

4.4 Main findings

4.4.1 *Summary and classification*

Table 4.8 presents a summary of the main findings of the results of the pregnancy outcomes. The rationale for the classification of the health outcomes is described in paragraph 4.4.2.

Table 4.8 Summary of results in the main model and classification of the association (n=285,809 for SGA and preterm, n=270,669 for LBW and Apgar; n=287,167 for congenital anomalies and infant mortality; primary outcomes in bold).

Outcome	OR	(95% CI)	Classification
Pregnancy outcomes			
SGA	**1.02**	**(0.98, 1.07)**	**Possible association**
Low BW (term)	**0.95**	**(0.85, 1.05)**	**No association**
Preterm (GA <37w)	**1.02**	**(0.96, 1.07)**	**Possible association**
Infant mortality (1st yr)	1.00	(0.83, 1.19)	No association
Ca-Any	1.05	(0.98, 1.13)	Probable association
CA-Nervous and senses system	1.15	(0.94, 1.41)	[1]
CA- Circulatory system	1.04	(0.90, 1.21)	[1]
CA-Tractus digestivus	1.07	(0.88, 1.30)	[1]
CA-Tractus respiratorius	1.20	(0.88, 1.65)	[1]
CA-Tractus urogenitalus	1.11	(0.96, 1.27)	[1]
CA-Skin and abdominal wall	1.05	(0.86, 1.29)	[1]
CA-Muscolo-skeletal system	1.10	(0.95, 1.28)	[1]
Apgar (ordinal)	0.90	(0.85, 0.95)	No association

[1] For the main findings only associations for 'any congenital anomalies' were considered due to the limited number of cases per subcategory.

4.4.2 *Rationale for the classification*

Effect estimates for **prematurity** were generally positive but did not reach statistical significance in the main model. However, this association increased and became statistically significant when the 4 municipalities with the lowest UFP exposure were excluded, in births with induced labour (including planned caesarean section) and after non-linear adjustment for EC or NO_2. In addition, associations between UFP-aviation and gestational age as continue outcome were statistically significant. Also, the association became borderline significant ($p<0.10$) when the population was restricted to mothers with a Dutch background, and in the higher exposure range end of the exposure response curves. At the lowest concentrations a decreasing, not biologically plausible, trend is observed for prematurity, which is reduced when the 4 municipalities with the lowest UFP exposure are excluded. We therefore classified the association between UFP and prematurity as a **'possible association'.**

For SGA, effect estimates were consistently elevated, but only reached borderline statistical significance in one of the sensitivity analyses (i.e.

excluding the 4 municipalities with the lowest average UFP exposure). We therefore classified the findings for SGA as a **'possible association'.**

For ***LBW***, effect estimates were generally below unity, but only became borderline statistically significant in one of the sensitivity analyses (after excluding mothers who lived in Amsterdam). We therefore classified the findings for LBW as **'no association'.**

We classified the associations between UFP from aviation and **infant mortality before age 1** as '**no association'**. Effect estimates were around unity and did not reach statistical significance in the main model, in the models adjusted for co-pollutants and the sensitivity analyses.

Associations with **congenital anomalies** were not significant but all positive in the main model. In general these associations persisted after adjustment for co-pollutants as well as in sensitivity analyses. Associations were sensitive to exclusion of the 4 municipalities with the lowest average UFP exposure, after which the association became statistically significant for the combined variable 'any anomaly' and (borderline) significant for the 3 categories of anomalies with the highest number of cases, i.e. urogenital anomalies and anomalies of the circulatory and muscolo-skeletal system. In addition, for several categories of anomalies, the fit of the model improved whilst effect estimates increased and became (borderline) significant when municipality was considered as a 'random effect'. Analyses that include the UFP-exposure during the second month as well as the third trimester, confirmed that the exposure during the second month is the most relevant exposure window. We therefore classified congenital anomalies as a "**probable association**".

For **Apgar** scores, we found significant inverse associations with UFP from aviation. When analyses were performed including municipality as random effect, as proxy for health care provider, or analyses excluding the 4 municipalities with the lowest average UFP exposure, results showed that the fit of the random effect model improved considerably and these associations were strongly driven by specific municipalities, including the 4 municipalities with the lowest average UFP exposures. After excluding these municipalities (as part of the sensitivity analyses), no significant associations with Apgar scores were observed. This is also observed in the exposure-response curves; excluding the 4 lowest exposed municipalities resulted in a reduction of the decrease of the effect estimate at the lowest concentration range. This indicates that there might be variability in assessment of Apgar between care providers, likely due to some subjective aspects of scoring (see also chapter 4.3.3). In addition, we considered a protective effect of UFP on a lower Apgar not biological plausible. Therefore, we classified associations with Apgar as **"no association"**.

4.4.3 Study specific aspects

4.4.3.1 Introduction

In this section we describe methodological aspect that are specific to the study presented in this chapter. More general aspects that apply to the study as a whole, such as exposure classification and adjustment for other air pollutants and noise, are addressed in chapter 7.

4.4.3.2 Classification of health outcomes

In this chapter, we studied associations between pregnancy outcomes and exposure to UFP from aviation at the residential address during pregnancy.

We included low birth weight, SGA and preterm birth, which are deliveries that occur at less than 37 weeks gestational age, as primary endpoints as these were most frequently studied in relation with air pollution. Gestational age and birth weight are considered as well-classified health outcomes; in the Netherlands, birth weight is registered for every birth and in over 95% of pregnancies, gestational age is certain, either confirmed by or based on an early ultrasound (www.perined.nl). SGA is used to determine whether birthweight is appropriate for the corresponding gestational age. It is often considered as a limitation that SGA infants may be small, yet simultaneously healthy as SGA is generally defined as a statistical description of a small neonate (i.e., birthweight a birth weight below the 10th percentile for gestational age). In our study, SGA was based on the Hoftiezer curves. Hoftiezer developed prescriptive birthweight charts, derived from a large population of Dutch infants without risk factors for SGA or excessive fetal growth, in order to improve distinction between normal and abnormal birthweight (Hoftiezer et al. 2018).

Information on mortality before age 1, congenital anomalies and Apgar scores was also available in this study. These were included as secondary endpoints as the available evidence of air pollution effects for these outcomes is limited (EPA, 2019). Congenital anomalies were available per organ system. We did not have ICD10-codes, so it was not possible to study more specific subtypes of anomalies. Apgar scoring is standard practice in obstetrics, and checks a baby's colour, heart rate, muscle tone, reflex irritability and breathing. It is a rapid method for evaluating new-born infants' health, usually given 1 minute and 5 minutes after birth and gives a short-term prognosis of new-born infants. On the long-term, low 5 minute Apgar scores are associated with cognitive outcomes and development impairment (Odd et al. 2007, Ehrenstein et al. 2009, Razaz et al. 2015). However, the Apgar score may be subject to inter- and intra-observer variability as some elements such as tone, colour, and reflex irritability can be subjective (O'Donnell, 2006).

4.4.3.3 Strengths and limitations

One of the strengths of our study is the large study population. We were able to include more than 285,000 births between 2006-2018, in a study area covering an area of 50 km x 56 km around Schiphol. Almost all (97%) births in this area were included so the present study can be considered as an unbiased representation of the total population of the study area. Moreover, the specific exposure window was well-defined,

i.e. during pregnancy and the three months before conception, which made exposure misclassification less likely. As monthly UFP-estimations were available, we were able to estimate exposure during the second month in relation to congenital anomalies. However, the applicability of the model we used to estimate exposure to UFP from aviation was only evaluated for half year average concentrations, therefore using second-month-exposure may be subject to more measurement error compared to studies that used long term exposure. However, we previously documented that 24-hour averaged modelled concentrations were highly correlated with daily measurements of particles smaller than 20 nm (as indicator of UFP from aviation), which were conducted at the schools of the panel study of the short-term effect component of the Schiphol Health study (Janssen et al, 2019).

Another strength of this study is that we had access to the full residential address histories and detailed information from perinatal database from hospital and midwife, exposure and on important potential confounders, such as maternal age, education, percentile of household income, and information regarding the socio-economic level of the residential neighbourhood.

Our analyses may still be suffering from residual confounding due to factors that were not available at individual level, such as genetic susceptibility, maternal stress and individual lifestyle factors, such as maternal smoking, alcohol consumption and body mass index (BMI). In chapter 6 analyses were performed in a sample of female participants of the Public Health Monitor with comparable distributions of age, educational level and migration background as the study population that was included in the pregnancy outcome study. In this subsample UFP from aviation was inversely related with smoking, alcohol consumption and overweight, indicating that women who were exposed to higher UFP levels from aviation generally had a healthier lifestyle. This suggests that not taking into account lifestyle factors could have resulted in an underestimation of associations between UFP and pregnancy outcomes in this study. Also, our exposure assessment was limited to home address during pregnancy; no information was available on time activity patterns, which can potentially result in exposure misclassification. Despite adjusting for municipality and area SES, also unexplained spatial heterogeneity might result in residual confounding. Another limitation of our study is that the number of children with congenital anomalies in our study area is limited as many congenital anomalies are rare, and we had no information regarding follow-up diagnoses beyond the delivery admission. Additionally, the infant mortality rate was low (0.8%/n=2,164). Most studies on infant mortality were limited to infants who died in the post-neonatal period (≥28 days after birth) because death before the post-neonatal period tended to occur from pregnancy complications (WHO 2015). The prevalence of post-neonatal mortality in the presence study was 0.03%/n=85 and therefore only mortality before the age of 1 was considered in our study.

We had no detailed information regarding the hospital or midwife that supervised the delivery, so we were not able to adjust for potential clustering of data within a health care provider. We expect that this mainly would affect Apgar scores, as elements of the score can be

subjective. Birth weight and gestational age are considered as more accurate and unbiased measures, although preterm birth, that can be the result of the decision for labour induction or caesarean section, can also differ per health care provider. Including municipality as random effect, as indicator of health care provider, changed associations between UFP-exposure and Apgar from significant and inverse to no associations, suggesting that Apgar scores associations were strongly driven by some municipalities. Associations between UFP-exposure and primary health endpoints and infant mortality were not affected by the inclusion of municipality as random effect.

4.5 Appendix

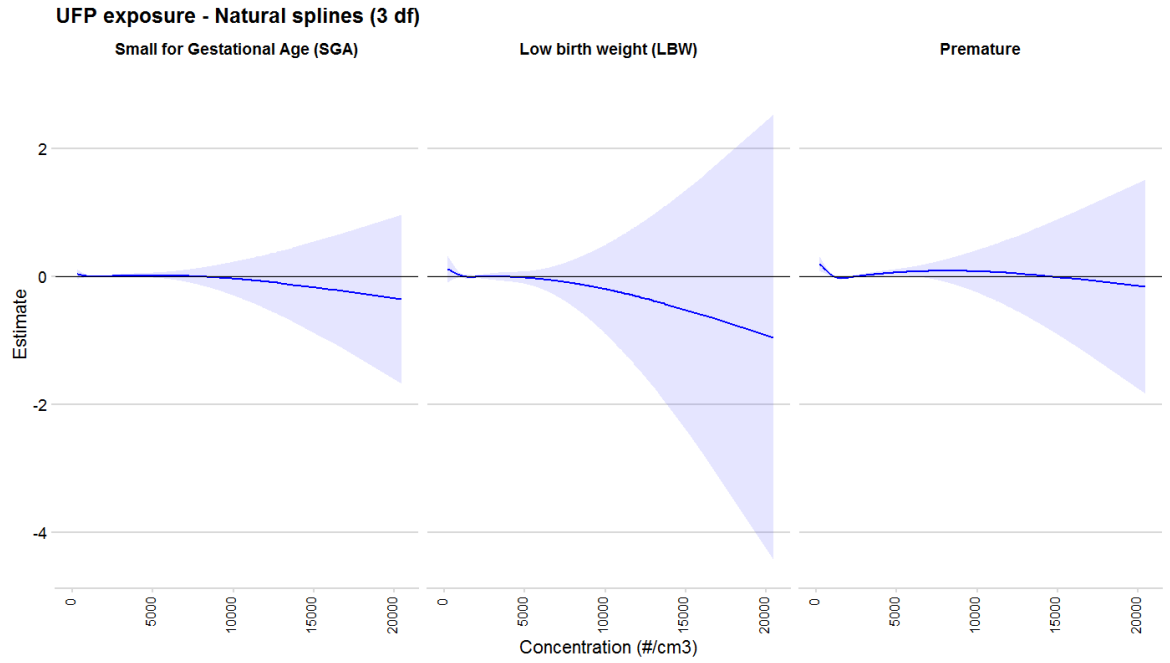


Figure A.4.1 Natural cubic splines (3 df) for associations between UFP from aviation and LBW, prematurity and SGA, full concentration range.

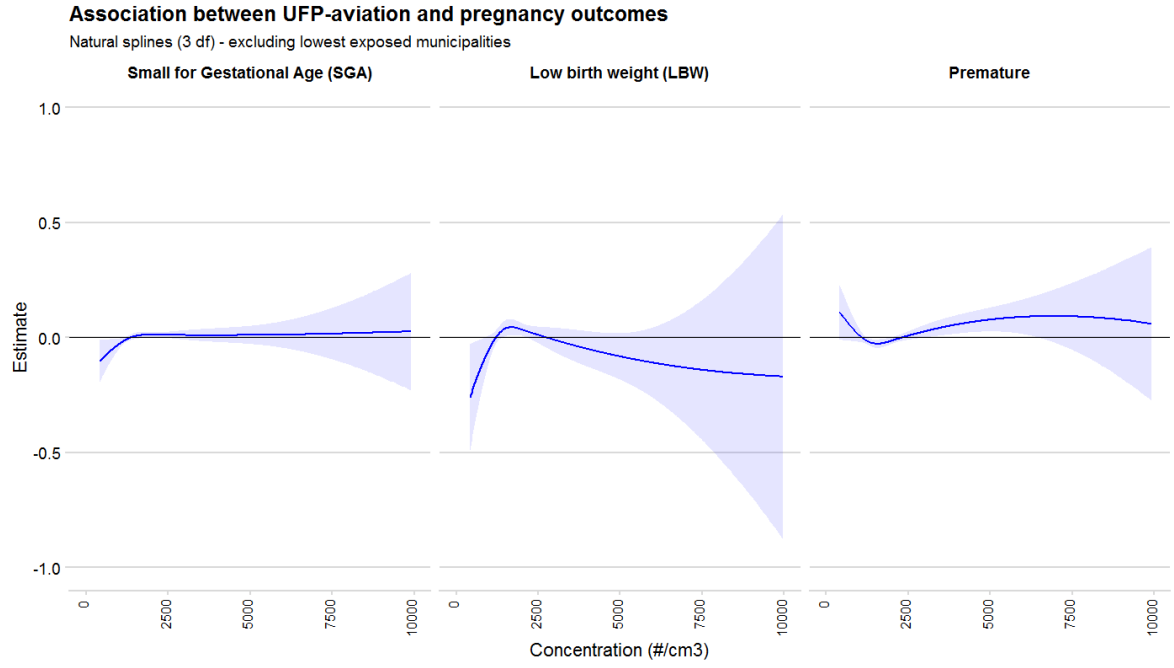


Figure A.4.2 Natural cubic splines (3 df) for associations between UFP from aviation and LBW, prematurity and SGA, excluding the 4 municipalities with the lowest average UFP exposure.

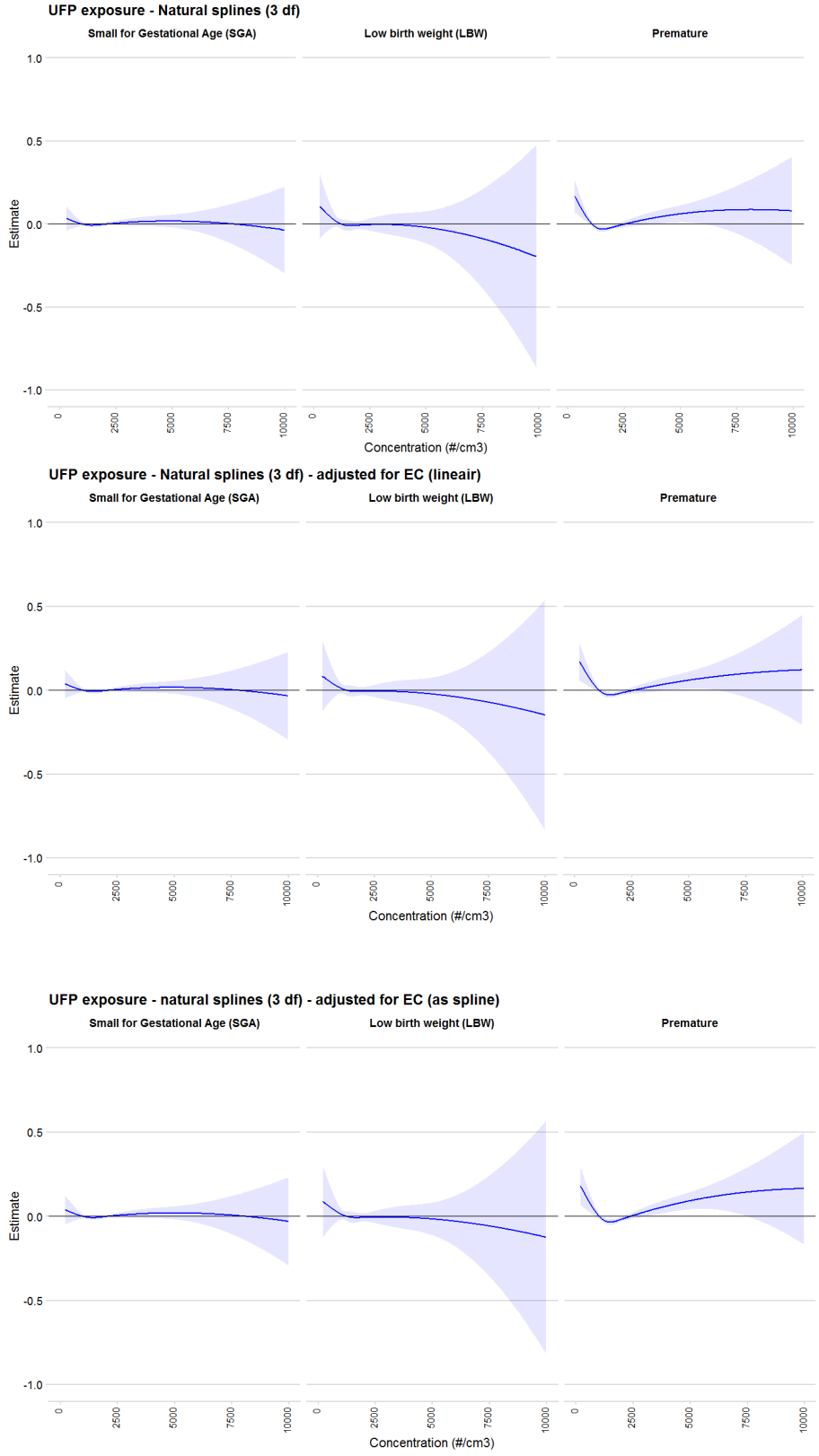


Figure A4.3a Natural cubic splines (3 df) for associations between UFP from aviation and SGA, LBW and preterm birth, without adjustment for EC (upper), adjust for EC as a linear term (middle) and adjusted for EC as a natural cubic splines (3 df).

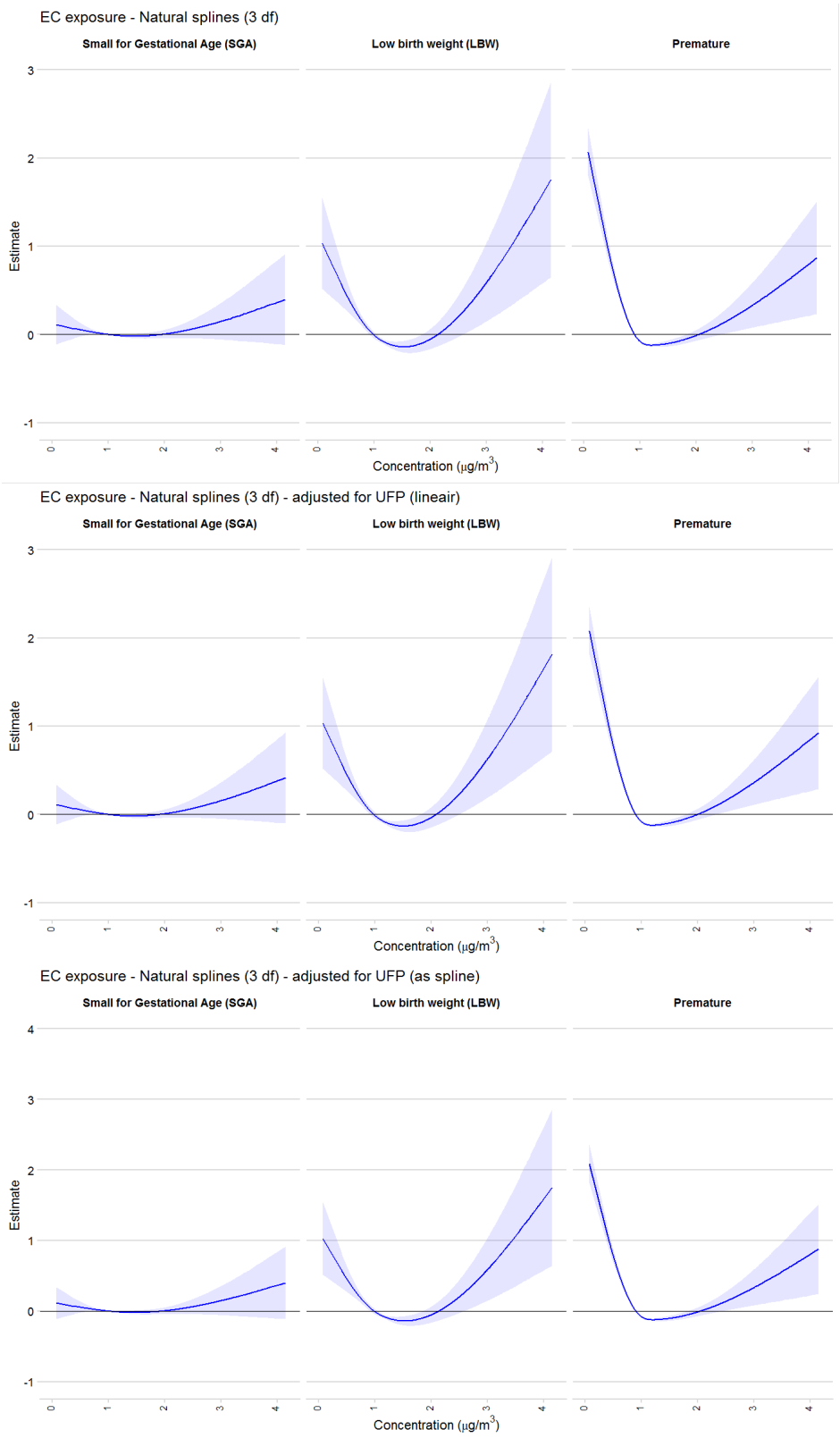


Figure A4.3b Natural cubic splines (3 df) for associations between EC and SGA, LBW and preterm birth, without adjustment for UFP from aviation (upper), adjust for UFP as a linear term (middle) and adjusted for UFP as a natural cubic splines (3 df).

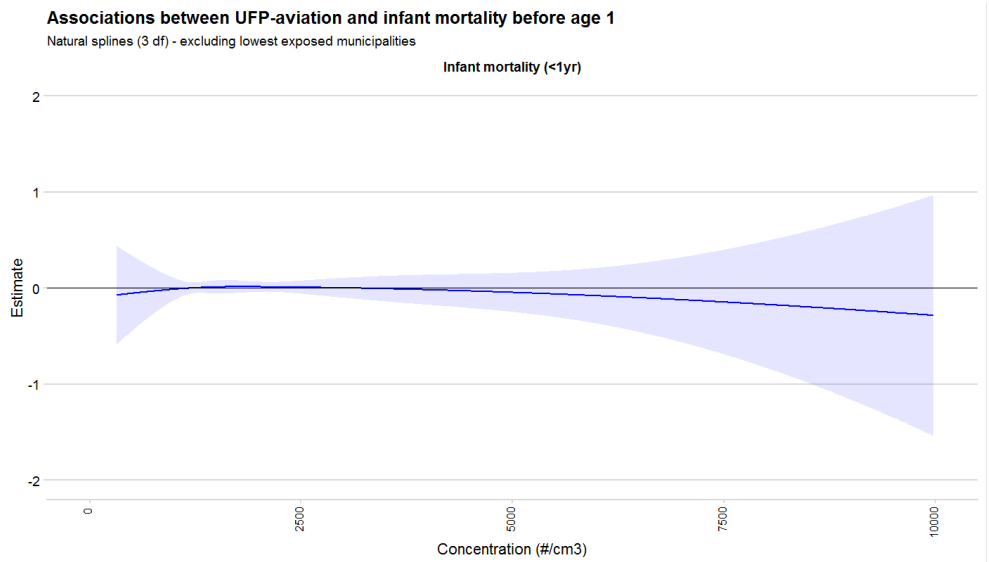


Figure A.4.3c Natural cubic splines (3 df) for associations between UFP from aviation and infant mortality, excluding the 4 municipalities with the lowest average UFP exposure.

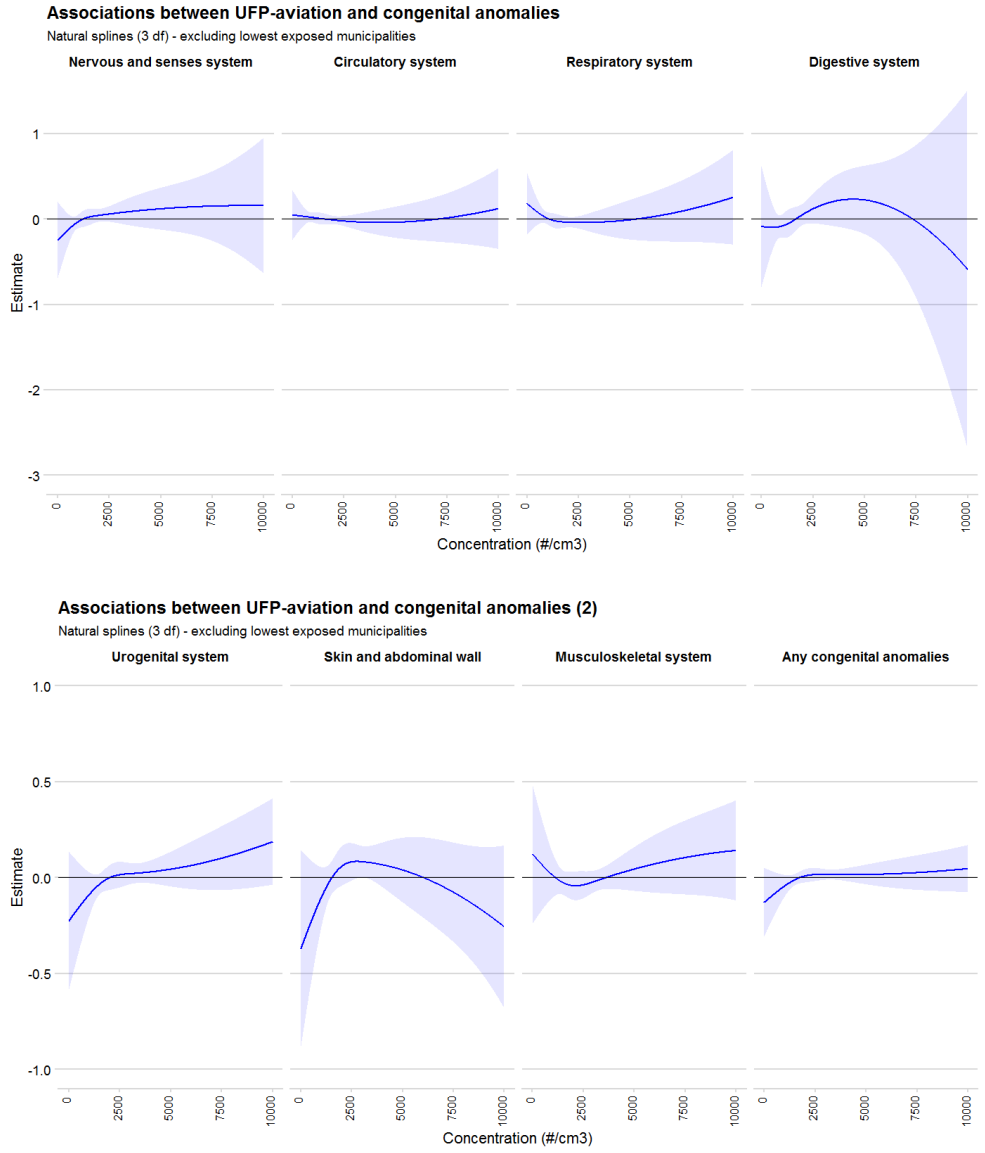


Figure A.4.4 Natural cubic splines (3 df) for associations between UFP from aviation and congenital anomalies, excluding the 4 municipalities with the lowest average UFP exposure.

Table A.4.5 Associations between congenital anomalies and exposure to UFP from aviation during the second month, and the second month and the third trimester mutually adjusted (n=285,530).

	OR (95% CI)			
	Exposure during month 2	Exposure during trimester 3	Exposure mutually adjusted (month 2 and trimester 3)	
Health outcome	**Month 2**	**Trimester 3**	**Month 2**	**Trimester 3**
Any congenital anomaly (CA)	1.05 (0.97- 1.13)	0.97 (0.88- 1.06)	1.08 (0.99- 1.18)	0.92 (0.83- 1.03)
CA-Nervous and senses system	1.13 (0.91- 1.41)	1.06 (0.81- 1.39)	1.14 (0.88- 1.48)	0.98 (0.71- 1.35)
CA- Circulatory system	1.03 (0.88- 1.20)	0.89 (0.73- 1.08)	1.11 (0.93- 1.33)	0.83 (0.67- 1.05)
CA-Tractus digestivus	1.05 (0.86- 1.27)	1.07 (0.85- 1.38)	1.02 (0.81- 1.29)	1.05 (0.80- 1.38)
CA-Tractus respiratorius	1.21 (0.88- 1.68)	1.24 (0.84- 1.82)	1.15 (0.78- 1.69)	1.14 (0.72- 1.80)
CA-Tractus urogenitalus	1.10 (0.95- 1.26)	1.02 (0.86- 1.21)	1.12 (0.95- 1.32)	0.95 (0.78- 1.17)
CA-Skin and abdominal wall	1.08 (0.88- 1.33)	0.86 (0.66- 1.12)	1.21 (0.95- 1.54)	0.77 (0.56- 1.04)
CA-Muscolo-skeletal system	1.10 (0.94- 1.28)	1.02 (0.60- 1.73)	1.12 (0.94- 1.35)	0.94 (0.75- 1.18)

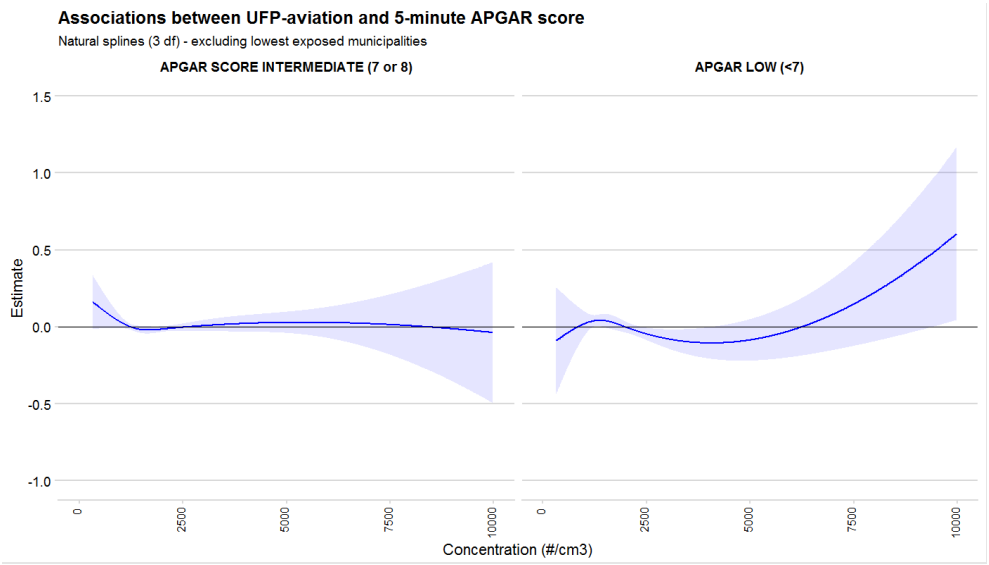


Figure A.4.6 Natural cubic splines (3 df) for associations between UFP from aviation and Apgar scores, excluding the 4 municipalities with the lowest average UFP exposure.

5 Dispensing of medication

5.1 Objectives

The overall objective of this study is to describe the association between long-term residential exposure to UFP from aviation and the first-time dispensing (incidence) of various groups of medication in various age groups.

5.2 Methods

5.2.1 Study design

We selected in total 11 different study populations to study the incidence of different medication groups in various age groups. All studies were designed as an administrative cohort study, starting on 1-1-2008 and ending 3112-2019. Eligible participants had to live in the study area that consists of the 31 municipalities that are fully included in the modelling area of UFP from aviation for 50 by 55 km around Schiphol Airport at 1-1-2018.

The information on the dispensing of medication is available per calendar year in so-called Dutch microdata available at CBS about the reimbursement of medication covered by the basic health insurance package in the Netherlands. In chapter 2 the organ systems that could potentially be affected by UFP were identified: the respiratory, the cardiovascular, the metabolic and the nervous system. The choice of the medication groups (medication for asthma/COPD, for heart disease, for hypertension, for diabetes, for Parkinson's disease, for dementia syndromes, for depression or for ADHD) are related to these organ systems and is described in more detail in paragraph 5.2.3.

5.2.2 Study population

The study populations consist of subjects between 0-5 years old, 6-12 years old, 6-19 years old, 14-19 years old, 20 years or older, or 40 years or older, depending on the medication group (see paragraph 5.2.3). The study population is an open cohort, meaning that subjects enter and leave the population at different points in time, throughout the study, between 1-1-2008 and31-12-2019. We retrospectively identified the participants. We initially selected all residents who lived within the study area on the 1st of January 2008. Additionally, we selected all newborns and new residents on the 1st of January of later calendar years, who fulfilled the age requirement for the study population. Entry in the cohorts after 2008 was allowed to maximise the number of children 0-5 years old. An exception was made for the cohorts for Parkinson's disease and Dementia; since it became clear that amongst later participants (whom on average were younger and had a shorter follow-up time) the incidence was very low. Given the low added value to the power (more than 97% of all cases occurred among participants that entered in 2008), we decided not to include additional subjects in these two cohorts after 2008. Household income was not yet available for newborns in 2019; we therefore decided not to include new participants in the cohort on medication for Asthma/COPD for the age group 0-5 years old in the calendar year 2019 .

The participants should not have used the medication of the medication group under study in the two calendar years before entering the study. Participants were also required have complete information on their residential history in the first calendar year of the study as well as in the 5 years before entering the study. We excluded subjects for whom the primary address was outside the study area in the first year of the study .

Since medication prescription practice may vary between family doctors and information on the family doctor was not available, we used district ("wijk") as surrogate assuming that the choice of the family doctor is based on the location of the residential address. Because, medication provided to patients in hospitals and nursing homes is not registered in the basic health insurance package, we formulated additional exclusion criteria for the study population. We excluded residents that did not live in the same district in the two years before the baseline as in the first calendar year of the study. Also, we excluded residents that lived more than 270 days in an institution in any of the two years before baseline or in the first calendar year of the study.

For children younger than 2 years old at baseline all above mentioned criteria on duration were replace by "from birth".

Subjects were censored at 31-12 of the concerning calendar year in case they deceased. Study participants were censored at 31-12 of the preceding calendar year in case of: the residential address with the longest duration in the calendar year is outside the study area or living more than 270 days in an institution in the calendar year.

The study ended for participant at 31-12-2019 or for a child or adolescent at 31-12 of the preceding calendar year if the child or adolescent no longer fulfilled the criterium for the age group at 1-1.

5.2.3 Health outcomes

Since 2006 health insurers provide yearly information to the National Health Care Institute (Zorginstituut Nederland) about the reimbursement of medication covered by the basic health insurance package for the so-called risk equalisation. The risk equalization compensates health insurers for differences in the composition of their insured population. Amongst other things, information about the number of patients with certain chronic diseases is used for the risk equalization. These patients are identified based on the medicines that are known to be prescribed for the disorder in question (pharmacy cost groups).

Data on the medication covered by the basic health insurance package is available for research at Statistics Netherlands for the period 2006-2019. The data is available on individual level, but in an aggregated form:

- The available information on medication provision is aggregated over a calendar year.
- Medicines are internationally classified according to the Anatomical Therapeutic Chemical Classification with defined daily doses (ATC/DDD system). Statistics Netherlands routinely provides the first 4 positions of the ATC code that consists of 7 letters and numbers.

Over the period 2006-2019, several pharmacy cost groups have been formulated in the framework of the risk equalisation. We initially selected the pharmacy cost groups that are related to the endpoints under study. Since the pharmacy cost groups are based on the 7 digit ATC codes they cannot be fully reconstructed on the available 4 digit ATC codes. Also, the definition of some of the pharmacy cost groups changed over time. We therefore identified all ATC-4 codes that were used in the pharmacy cost groups of interest during the period 2006-2019 and combined them in medication groups that were related to the composition of the pharmacy cost groups. We will use the term medication groups in this report to avoid possible confusion with (the composition of) the pharmacy cost groups.

The medication groups and their composition are described in Table 5.1 and in Table 5.2.

Table 5.1 Medication groups used for the study (primary endpoints).

Outcome of interest	Medication group	ATC-4 code	ATC-4 description	Age group(s)
Respiratory	Asthma/COPD	R03A R03B R03C R03D	Adrenergics, inhalants Other drugs for obstructive airways diseases, inhalants Adrenergics for systematic use Other systematic drugs for obstructive airway diseases	0-5 years 6-19 years 20 years and older
Cardiovascular	Heart diseases	C01A C01B C01C C01D C01E C03C	Cardiac glycosides Antiarrhythmics, class I and III Cardiac stimulants excl. glycosides Vasodilators used in cardiac diseases Other cardiac preparations Heigh ceiling diuretics	40 years and older
Cardiovascular	Hypertension	C02A C02C C02D C02K C03A C03B C03D C03E C07A C07B C07C C07F C08C C08D C08G C09A C09B C09C	Antiadrenergic agents, centrally acting Antiadrenergic agents, peripherally acting Arteriolar smooth muscle, agents acting on Other antihypertensives Low-ceiling diuretics, thiazides Low-ceiling diuretics, excl. thiazides Potassium-sparing agents Diuretics and potassium-sparing agents in combination Beta blocking agents Beta blocking agents and thiazides Beta blocking agents and other diuretics Beta blocking agents, other combinations Selective calcium channel blockers with mainly vascular effects Selective calcium channel blockers with direct cardiac effects Calcium channel blockers and diuretics	20 years and older

Outcome of interest	Medication group	ATC-4 code	ATC-4 description	Age group(s)
		C09D C09X	Ace inhibitors, plain Ace inhibitors, combinations Angiotensin ii receptor blockers (arbs), plain Angiotensin ii receptor blockers (arbs), combinations Other agents acting on the renin-angiotensin system	
Metabolic	Diabetes	A10A A10B	Insulins and analogues Blood glucose lowering drugs, excl insulins	20 years and older
Nervous system	Parkinson's Disease	N04B	Dopaminergic agents	40 years and older

Table 5.2 Medication groups used for the study (secondary endpoints).

Outcome of interest	Medication group	ATC-4 code	ATC-4 description	Age group(s)
Nervous system	Dementia syndromes	N06D	Anti-dementia drugs	40 years and older
	Anti-depressants	N06A	Anti-depressants	12-19 years 20 years and older
	ADHD	NO6B	Psychostimulants, agents used for ADHD and nootropics	6-14 years old

All identified ATC-4 codes belonged to one medication group, with the exception of C09D. In the period 2006-2019, CO9D was part of the medication group hypertension and it was also included in the medication group hearth disease in 2018 and 2019. We only included C09D in the medication group for hypertension to avoid overlap between these two medication groups.

We make a distinction between primary and secondary endpoints in the tables 5.1 and 5.2. For the primary endpoints we expected that there is sufficient similarity between the incidence of medication use and the onset of the treatment of the disorder based on the study of Slobbe et al. (2019), or we already had previous experience with the medication group in cross-sectional studies (hypertension). We considered treatment for dementia syndromes or for psychological complaints as a secondary endpoint, since the agreement was less in the study of Slobbe et al. or was unknown (ADHD).

We distinguish relevant age groups for the medication groups (see Table 5.1 and 5.2).

- The Dutch College of General Practitioners distinguishes in their guideline for asthma between children up to six years of age and children over six years of age. Persons aged 20 years and over may be affected by other risk factors such as occupational exposure to air pollution and smoking habits.
- For medication for high blood pressure and for diabetes, we selected adults aged 20 and over. For medication for heart disease, for Parkinson's disease and for dementia syndromes we selected adults from the age of 40. The reason for the age limit is that medication use for these conditions at a younger age is rare
- For anti-depressants and ADHD, that are used by children and adolescents as well, we initially followed the age groups defined for asthma (6-19 year old and 20 years and older). Based on the incidence we later redefined the age groups for anti-depressants to 12-19 year old and 20 years and older and for ADHD to 6-14 year old.

In order to calculate the incidence in a certain calendar year, information about the medication dispensed in the previous calendar year is required to determine whether a new use has occurred. In this case, there is a 'run-in' period of one year. Some medication such as those for respiratory diseases are not used (or dispensed) annually. When the run-in time is extended, the probability increases that there is actually a new user instead of the provision of a repeat prescription. For this reason, we applied a run-in of two years for all medication groups. Consequently we also formulated criteria for having lived in the same district and not in an institution in the two-years period of the run-in time before the baseline (see paragraph 5.2.2). For new-borns, the (two) years before birth are considered years of no medication use so children can become incident in the first or second year of their life.

The calendar year of the event refers to first time use of medication of the specific medication group in the concerning calendar year, except for Parkinson's disease. When there are signs of Parkinson's disease dopaminergic agents may be prescribed temporarily to see if symptoms

improve and other causes of the symptoms can be excluded. Therefore, the calendar year of the event was defined as the second consecutive calendar year that the medication from the group Parkinson's disease was used. As a consequence the incidence of Parkinson's disease in 2008 is zero.

5.2.4 Assessment of exposure to UFP from aviation

We describe in detail the modelling of exposure to UFP from aviation in Chapter 2.5. For the current study, we calculated annual averaged UFP contributions for the period 2003-2019 for a grid of 250*250 meter, covering the whole study area. This allows calculation of different exposure windows, including incorporating residential history.

We also calculated average concentrations for 2-, 3- and 5-year multi-annual averages, in order to investigate whether these may reflect exposure better than 1-year averages. The idea behind the 2-year average is that, if there is an effect within a few months, medication given at the beginning of the year may be related to the concentration in the previous calendar year and medication given at the end of the year to the concentration in the current calendar year (Houthuijs et al., 2022). Additionally, we also calculated the annual average of hours per month with UFP concentrations above 66,667 #/cm3 (see 2.5.4), in order to get an indication of possible peak exposures.

5.2.5 Potential confounders

At baseline, we recorded age, gender, migration background, district and neighbourhood codes, marital status (only applied in the age groups 20 years or older and 40 years or older) and household income and socio-economic status variables at the neighbourhood level, both aggregated per calendar year. For the whole duration of the follow-up, we record demographic information at the individual level (residential mobility and marital status changes during the study period), at the household level (household income aggregated per calendar year) and at the neighbourhood level (percentage of low, middle or high education, percentage unemployment, percentage of beneficiary, etc. dynamic). For details about the confounders, we refer to paragraph 2.6.

Given the missing values of household income we calculated the median of the series of available annual household incomes expressed as percentile of the household income distribution in the Dutch population. The median was used as time-fixed covariate after being divided in 10 categories based on percentiles within the study population ≤ 1, >1-5, >5-10, 10-25, 25-50, 50-75, 75-90, 90-95, 95-99 and >99 percentile).

The area level socio-economic status variables were divided per calendar year in quintiles based on the distribution within the study population.

We used the geographical lay-out of the districts in 2008 (the baseline year for most study subjects) as classification of the random effect for the calendar years 2008-2019, since the geographical area of a district may change over time due to administrative changes. A priori we formulated the criterion that the minimum number of inhabitants in a district should be 750 in 2008 to avoid a small number of events in the random effect that could hamper the fitting of the shared frailty model.

As a consequence, we combined in a limited number of cases a district that did not full fill the criterion with an adjacent district in the same random effect.

5.2.6 Other air pollutants and transportation noise

We included annual average concentrations of PM2.5, NO_2, and EC as co-pollutants in our study. More information on co-pollutants modelling methodology is provided in Chapter 2.7.

We included annual average aviation noise levels from Schiphol, as well as road-traffic and railway noise exposures. More information on noise exposure assessment is available in Chapter 2.7.

5.2.7 Statistical analyses

5.2.7.1 Main analyses

We used Cox-proportional hazards regression models. Within a specific combination of medication and age group, the first incidence is noted as the only event. The participants were subsequently censored at the end of the concerning calendar year; we did not investigate recurrent events. Censoring time was defined as occurrence of one of residential mobility, death or replacement to a nursing home and was considered statistically independent of the time to event, given covariates.

We examined time-to-event in relation to the a priori selected set of explanatory variables, with exposure variables measured over time (time-dependent).

We investigated the assumptions underlying the Cox model by studying plots of the non-parametric Kaplan-Meier estimator and plots of the logarithm of the cumulative hazard against age in the presence of categorical covariates. For continuous covariates, we used the landmark approach which allows to estimate the hazard ratio as a function of time and therefore detect departures from the proportionality assumption.

We started with a model with age as underlying timescale and with 3 year periods as strata. The choice of time scale was motivated as follows. The Kaplan-Meier estimator of the survival curve, with age as the primary time scale, revealed that the events occur across the full range of ages in all medication studies. Handling age as primary time scale implies that the adjustment for the main effect of age in the Cox proportional hazards model is done non-parametrically, without parametric constrains on the shape of the baseline hazards. Follow-up time or calendar time as primary time scales proved as weaker determinants of the hazard rates than age, therefore they were dealt with jointly through modelling of the proportional hazards regression model.

Subsequently, we added the a priori selected individual covariates and household income. As area level confounders, we selected a priori the percentage of high education, the mean household income and percentage of inhabitants with a non-western migration background within a neighbourhood, based on the experiences in the mortality and birth outcomes substudies. The statistical analyses were carried out separately for men and women.

Lastly, district was added as Gamma shared frailty in the model and it was evaluated whether the explained additional variance justified the application of a frailty model. The shared frailty did contribute to the model fit, except for the medication group Parkinson's disease amongst men. For this combination we used a model without shared frailty and calculated robust standard errors to take into account that participants within districts are not fully independent observations.

In addition to the annual average UFP exposure with lag0 we evaluated concentrations of 2, 3 and 5 years moving averages (the calendar year of interest is included, so without a lag-year). The most relevant exposure indicator for UFP was selected for the subsequent analyses (with an annual average exposure over one year with lag0 as default).

We investigated whether the main predictor variable for UFP from aviation exhibits non-linear effects. To this goal, we used natural cubic splines of the UFP concentration with three degrees of freedom. We divided the follow-up interval in two subintervals, corresponding to 50% of events respectively. Together with the boundary values of the UFP range, this breaking point defined the knots of the natural cubic splines. We will show plots of the associated effects on the log-hazard scale implied by our choice of spline functions. The underlying model comprised the joint effect of confounders and the frailty term.

We report the estimate of the relevant UFP indicator using a priori defined models with increasing covariate adjustment:

- Model 1: age as underlying time scale with 3 year periods as strata, separate analysis for men and women.
- Model 2: model 1 + individual covariates and household income.
- Model 3: model 2 + selected indicators for area-level SES.
- Main model: model 3 + shared frailty.

5.2.7.2 Multi-exposure models

For all cohorts, residential concentrations of PM2.5, NO_2, and EC were available for the same exposure windows as for UFP from aviation. Due to correlations between the air pollutants, we included PM2.5, NO_2, and EC separately in two-pollutant models, as well as a combination of PM2.5 and NO_2.

Exposure to transport noise (aviation from Schiphol, road, and rail traffic) may contribute to the risk of some of the health endpoints under study for UFP and was therefore included as a potential confounder in multi-pollutant models, except in the cohorts with medication for asthma/COPD and ADHD. We adjusted UFP from aviation for all available noise variables; we made separate models for 24-hour noise (L_{den}) and night time noise (L_{night}). We also combined PM2.5 and NO2 with L_{den} or with L_{night} from the various noise sources. We assigned a value of 53 dB L_{den} to all noise levels < 53 dB L_{den} and a value of 43 dB L_{night} to all noise levels < 43 dB L_{night}.

For details on the multi-exposure models, we refer to paragraph 2.10.1.

5.2.7.3 (Other) sensitivity analyses and stratifications

We carried out the following sensitivity analyses and stratifications:

- Urbanization (stratification, 2 strata (1+2 and ≥3).
- Exclusion of Amsterdam.
- Exclusion of three municipalities (Velsen, Beverwijk and Heemskerk) around a major industrial source in the IJmond region.
- Limiting the statistical analysis to participants with a Dutch background.
- Evaluate peak exposure to UFP from aviation by using the number of hours per year above 66,667 #/cm^3 (instead of an annual average concentration).
- Exclusion of the four municipalities with the lowest average exposure to UFP from aviation.

5.3 Results

5.3.1 Study populations, health outcomes and covariates

We defined in total 11 different study populations, each for a specific combination of medication and age group (see Table 5.1).

The upper half of Table 5.3 describes the selection process of the study populations of 40 years and older for three medication groups: heart disease, Parkinson's disease (both primary endpoints) and dementia syndromes (secondary endpoint).

The total number of unique residents of 40 years or older at January 1 2008 or on January 1 of subsequent years was 1,447,545 subjects.

We excluded residents from the study population in case they already used medication for the group under study in the two years before baseline, their residential history was incomplete, the address where they lived the longest in the first study year was outside the study area or they changed districts or lived in an institute in the baseline year or in the two years before baseline. In addition they were excluded due to missing covariates which was almost exclusively related to the missing of the complete series of household income. In case of missingness, about 90% of the subjects would have participated only one calendar year and about 95% a maximum of two years in the study.

The second part of Table 5.3 describes in which calendar year subjects entered the study, the total number of person years, the cumulative incidence and the reason for censoring. The reason for censoring refers to the event that occurred first in time.

The majority of the participants in the cohort for heart disease enters the study in 2008. About 25% of the study population enters in a later year which are mainly residents that have become 40 years old so fulfil the inclusion criterion for the age range. For Parkinson's disease and dementia syndromes, only participation in 2008 was allowed.

Table 5.3 Selection of the study populations of 40 years and older (medication for heart disease, for Parkinson's disease and for dementia syndromes).

Characteristics	heart disease N (%)	Parkinson's disease N (%)	dementia syndromes N (%)
Living in study area	1,447,545	1,447,545	1,447,545
Excluded	363,329	574,445	572,038
Medication use in two years before baseline	101,147	7,804	3,262
Unknown address in five years before baseline	88,282	88,850	88,890
Longest address in year of entry outside study area	14,167	14,577	14,593
Change of district in two years before baseline	133,444	142,183	142,554
In institute in two years before baseline	10,310	14,037	14,172
In institute in year of entry	1,257	1,920	1,954
Missing co-variates	14,722	18,522	18,700
Restricted to entry in 2008	0	287,550	287,913
Remaining	1,084,216	872,100	875,507
Year of entry			
2008	799,099 (73.7)	872,100 (100)	875,507 (100)
2009	28,192 (2.6)		
2010	30,015 (2.8)		
2011	29,425 (2.7)		
2012	28,203 (2.6)		
2013	27,226 (2.5)		
2014	25,416 (2.3)		
2015	24,705 (2.3)		
2016	23,127 (2.1)		
2017	23,171 (2.1)		
2018	22,823 (2.1)		
2019	22,814 (2.1)		
Person-years	9,621,031	9,229,895	9,262,348
Incidence	153,570 (14.2)	8,989 (1.0)	12,288 (1.40)
Incidence per year	(1.60)	(0.10)	(0.13)
Censored			
Moved outside study area	76,393	63,968	63,853
Moved to institute	16,245	25,556	23,873
Deceased	61,795	127,621	125,938

Table 5.4 describes the distribution of the covariates at baseline in the study population 40 years and older.

Since residents that had turned 40 years of age may become eligible for the study population in the period 2009-2019, the study population consists of almost 40% of subjects aged 40 to 45 years old. The majority is married or have an official partnership; about three quarters of the population has a Dutch background.

Table 5.4 Characteristics at baseline of the study populations of 40 years and older (medication for heart disease, for Parkinson's disease and for dementia syndromes).

Individual Covariates	heart disease N (%)	Parkinson's disease N (%)	dementia syndromes N (%)
Study population	1,084,216	872,100	875,507
Gender			
Males	522,242 (48.2)	418,608 (48.0)	419,913 (48.0)
Females	561,974 (51.8)	453,492 (52.0)	455,594 (52.0)
Age (years)			
40-44	428,783 (39.6)	145,565 (16.7)	145,731 (16.7)
45-49	138,612 (12.8)	141,528 (16.2)	141,752 (16.2)
50-54	119,981 (11.1)	124,747 (14.3)	125,097 (14.3)
55-59	109,786 (10.3)	116,509 (13.4)	116,887 (13.4)
60-64	97,579 (9.0)	106,190 (12.2)	106,705 (12.2)
65-69	66,360 (6.1)	75,359 (8.6)	75,858 (8.7)
70-74	49,811 (4.6)	59,662 (6.8)	60,171 (6.9)
75-79	37,410 (3.5)	48,689 (5.6)	49,038 (5.6)
80-84	22,891 (2.1)	32,818 (3.8)	33,137 (3.8)
85-89	10,098 (0.9)	16,025 (1.8)	16,120 (1.8)
≥ 90	2,905 (0.3)	5,008 (0.6)	5,011 (0.6)
Marital status			
Married/living together	630,638 (58.2)	527,446 (60.5)	529,655 (60.5)
Unmarried	258,388 (23.8)	147,412 (16.9)	147,753 (16.9)
Divorced	134,372 (12.4)	120,204 (13.8)	120,549 (13.8)
Widowed	60,818 (5.6)	77,038 (8.8)	77,550 (8.9)
Migration background			
Dutch	795,089 (73.3)	669,722 (76.8)	672,574 (76.8)
Netherlands Antilles	7,800 (0.72)	5,453 (0.6)	5,472 (0.6)
Suriname	42,788 (4.0)	32,452 (3.7)	32,522 (3.7)
Turkey	27,587 (2.5)	17,013 (2.0)	17,060 (2.0)
Morocco	33,064 (3.1)	19,869 (2.3)	19,925 (2.3)
Other, western	127,813 (11.8)	96,696 (11.1)	97,005 (11.1)
Other, non-western	50,075 (4.6)	30,895 (3.5)	30,949 (3.5)
Household income			
≤ 1 percentile	12,835 (1.2)	7,575 (0.9)	7,602 (0.9)
>1-5 percentile	45,997 (4.2)	33,062 (3.8)	33,141 (3.8)
>5-10 percentile	52,276 (4.8)	43,033 (4.9)	43,197 (4.9)
>10-25 percentile	164,589 (15.2)	145,735 (16.7)	146,584 (16.7)
>25-50 percentile	273,751 (25.3)	225,659 (25.9)	226,760 (25.9)
>50-75 percentile	262,045 (24.2)	207,442 (23.8)	208,072 (23.8)
>75-90 percentile	157,724 (14.6)	128,551 (14.7)	128,894 (14.7)
>90-95 percentile	48,398 (4.5)	34,852 (4.0)	34,938 (4.0)
>95-99 percentile	52,103 (4.8)	36,146 (4.1)	36,246 (4.1)
>99 percentile	14,498 (1.3)	10,045 (1.2)	10,073 (1.2)

Table 5.5 and 5.6 describe the selection and the characteristics of the populations of 20 years and older for studying medication for asthma/COPD, for diabetes, for hypertension and for depression.

The total number of unique residents of 20 years or older on January 1 2008 or on January 1 of subsequent years was 2,448,273 subjects.

Almost half of this population was excluded for the study. A relatively large number of residents were excluded since their residential address in the 5 years before the study was unknown. This number reflects the presence of relatively highly educated migrants who work mainly for internationally oriented companies and international students that have a strong preference for living in the city. Amsterdam is a particular favourite. Also, a large number of residents moved to a residential address in another district which can be explained by the residential mobility of the age group 20 to 40 years old. The main reason for censoring in the age group 20 years and older is moving to a residential address outside the study area.

Due to the exclusion of international knowledge workers and students and the residential mobility of the younger part of the population, the age distribution of the study population is more in balance than in the study population of 40 years or older. The four study populations consist of about 20% of subjects aged 20 to 25 years old. About 72% of the population has a Dutch background (see Table 5.6).

Table 5.7 and 5.8 describe the selection and the characteristics of the study populations for medication for asthma/COPD (0-5 years and 6-19 years), for depression (12-19 years) and for ADHD (6-14 years).

The total number of unique residents on 1 January 2008 or on 1 January of subsequent years varies between the medication groups due to the different criteria for the age of the population.

The main reason for censoring is that the participant did not fulfil the age criteria anymore. For asthma/COPD and depression, the majority of these participants will be followed further in the study populations for the next age range (6-19 years or 20 years and older).

We did not consider marital status as a covariate in this age group given the very small number of adolescents that were married, divorced or widowed.

Table 5.5 Selection of the study populations of 20 years and older (medication for asthma/COPD, for diabetes, for hypertension and for depression).

Characteristics	asthma/ COPD N (%)	hyper- tension N (%)	diabetes N (%)	depression N (%)
Living in area	2,448,273	2,448,273	2,448,273	2,448,273
Excluded	1,133,493	1,267,467	1,089,499	1,069,567
Medication use in two years before baseline	202,542	345,156	82,955	116,056
Unknown address in five years before baseline	391,060	390,965	392,914	391,976
Longest address in year of entry outside study area	29,068	29,450	31,037	30,274
Change of district in two years before baseline	471,985	472,358	503,695	490,953
In institute in two years before baseline	13,247	9,070	13,418	13,131
In institute in year of entry	1,712	1,185	1,765	1,707
Missing co-variates	23,879	19,281	23,710	25,470
Remaining	1,314,780	1,180,806	1,398,774	1,378,706
Year of entry				
2008	1,135,578 (86.4)	994,465 (84.2)	1,206,473 (86.3)	1,188,499 (86.2)
2009	14,886 (1.1)	15,472 (1.3)	16,027 (1.1)	15,860 (1.1)
2010	15,341 (1.2)	15,930 (1.4)	16,530 (1.2)	16,376 (1.2)
2011	16,302 (1.2)	16,954 (1.4)	17,599 (1.3)	17,442 (1.3)
2012	16,486 (1.3)	17,095 (1.5)	17,741 (1.3)	17,573 (1.3)
2013	16,567 (1.3)	17,188 (1.5)	17,774 (1.3)	17,584 (1.3)
2014	16,318 (1.2)	16,874 (1.4)	17,502 (1.3)	17,306 (1.3)
2015	16,050 (1.2)	16,640 (1.4)	17,203 (1.2)	16,992 (1.2)
2016	15,722 (1.2)	16,454 (1.4)	16,878 (1.2)	16,686 (1.2)
2017	16,802 (1.3)	17,502 (1.5)	17,932 (1.3)	17,733 (1.3)
2018	17,121 (1.3)	17,845 (1.5)	18,304 (1.3)	18,081 (1.3)
2019	17,607 (1.3)	18,387 (1.6)	18,811 (1.3)	18,574 (1.4)
Person-years	11,899,027	10,255,095	13,513,773	12,705,018
Incidence	204,718 (15.6)	262,470 (22.2)	67,489 (4.8)	171,897 (12.5)
Incidence per year	(1.72)	(2.56)	(0.50)	(1.35)
Censored				
Moved outside study area	147,867	142,210	166,860	154,741
Moved to institute	23,319	11,300	25,361	22,687
Deceased	82,199	34,269	103,531	101,504

Table 5.6 Characteristics at baseline of the study populations of 20 years and older (medication for asthma/COPD, for hypertension, for diabetes and for depression).

Individual Covariates	**asthma/COPD N (%)**	**hypertension N (%)**	**diabetes N (%)**	**depression N (%)**
Study population	1,314,780	1,180,806	1,398,774	1,378,706
Gender				
Males	653,623 (49.7)	591,236 (50.1)	681,897 (48.8)	686,637 (49.8)
Females	661,157 (50.3)	589,570 (49.9)	716,877 (51.3)	692,069 (50.2)
Age (years)				
20-25	249,384 (19.0)	259,779 (22.0)	267,401 (19.1)	264,028 (19.1)
25-29	75,774 (5.8)	79,265 (6.7)	80,920 (5.8)	78,136 (5.7)
30-34	94,975 (7.2)	99,217 (8.4)	101,945 (7.3)	97,527 (7.1)
35-39	125,259 (9.5)	130,176 (11.0)	135,202 (9.7)	128,619 (9.3)
40-44	132,331 (10.1)	133,948 (11.3)	143,115 (10.2)	135,194 (9.8)
45-49	127,630 (9.7)	122,756 (10.4)	137,511 (9.8)	130,112 (9.4)
50-54	111,654 (8.5)	98,739 (8.4)	119,016 (8.5)	114,230 (8.3)
55-59	103,599 (7.9)	83,325 (7.1)	108,874 (7.8)	107,269 (7.8)
60-64	93,553 (7.1)	67,232 (5.7)	96,878 (6.9)	99,279 (7.2)
65-69	65,065 (5.0)	42,076 (3.6)	66,924 (4.8)	71,100 (5.2)
70-74	50,378 (3.8)	27,713 (2.3)	51,911 (3.7)	56,403 (4.1)
75-79	40,243 (3.1)	18,702 (1.6)	42,011 (3.0)	45,989 (3.3)
80-84	27,276 (2.1)	11,017 (0.9)	28,521 (2.0)	31,002 (2.3)
85-89	13,375 (1.0)	5,092 (0.4)	14,048 (1.0)	15,082 (1.1)
≥ 90	4,284 (0.3)	1,769 (0.2)	4,497 (0.3)	4,736 (0.3)
Marital status				
Married/living together	581,042 (44.2)	490,933 (41.6)	616,137 (44.0)	613,570 (44.5)
Unmarried	551,580 (42.0)	555,398 (47.0)	588,034 (42.0)	571,879 (41.5)
Divorced	116,984 (8.9)	100,167 (8.5)	126,564 (9.1)	121,532 (8.8)
Widowed	65,174 (5.0)	34,308 (2.9)	68,039 (4.9)	71,725 (5.2)
Migration background				
Dutch	949,753 (72.2)	838,529 (71.0)	1,016,082 (72.6)	997,166 (72.3)
Netherlands Antilles	11,144 (0.85)	10,416 (0.9)	11,678 (0.8)	11,885 (0.9)
Suriname	59,664 (4.5)	53,575 (4.5)	60,962 (4.4)	63,465 (4.6)
Turkey	41,000 (3.1)	39,712 (3.4)	43,477 (3.1)	41,640 (3.0)
Morocco	50,039 (3.8)	49,891 (4.2)	51,197 (3.7)	51,321 (3.7)
Other, western	137,939 (10.5)	125,904 (10.7)	147,286 (10.5)	145,219 (10.5)
Other, non-western	65,241 (5.0)	62,779 (5.3)	68,092 (4.9)	68,010 (4.9)
Income				
≤ 1 percentile	13,695 (1.0)	12,878 (1.1)	18,673 (1.3)	14,077 (1.0)
>1-5 percentile	58,300 (4.4)	47,850 (4.1)	55,807 (4.0)	58,922 (4.3)
>5-10 percentile	67,257 (5.1)	59,165 (5.0)	71,471 (5.1)	67,617 (4.9)
>10-25 percentile	189,962 (14.5)	177,905 (15.1)	203,751 (14.6)	206,818 (15.0)
>25-50 percentile	336,907 (25.6)	301,223 (25.5)	349,839 (25.0)	350,775 (25.4)
>50-75 percentile	318,288 (24.2)	285,627 (24.2)	349,400 (25.0)	334,754 (24.3)
>75-90 percentile	193,707 (14.7)	166,776 (14.1)	205,784 (14.7)	203,054 (14.7)
>90-95 percentile	70,589 (5.4)	66,769 (5.7)	69,530 (5.0)	73,744 (5.3)
>95-99 percentile	52,508 (4.0)	49,695 (4.2)	60,424 (4.3)	54,770 (4.0)
>99 percentile	13,567 (1.0)	12,918 (1.1)	14,095 (1.0)	14,175 (1.0)

Table 5.7 Selection of the study populations for medication for asthma/COPD (0-5 years and 6-19 years), for depression (12-19 years) and for ADHD (6-14 years).

Individual Covariates	**asthma/ COPD *0-5 years* N (%)**	**asthma/ COPD 6-19 years N (%)**	**depression 12-19 years N (%)**	**ADHD 6-14 years N (%)**
Living in area	452,132	692,512	527,915	499,020
Excluded	94,185	237,882	153,037	88,585
Medication use in two years before baseline	65,850	65,196	1,789	5,353
Unknown address in five years before baseline	219	66,809	46,745	36,819
Longest address in year of entry outside study area	1,277	7,483	5,009	6,411
Change of district in two years before baseline	16,160	94,313	82,407	39,776
In institute in two years before baseline	137	331	381	197
In institute in year of entry	-	36	25	28
Missing co-variates	10,696	3,714	16,681	2,045
Remaining	357,793	454,630	374,878	408,391
Year of entry				
2008	118,882 (33.2)	253,320 (55.7)	154,749 (41.3)	181,699 (44.5)
2009	24,027 (6.7)	18,293 (4.0)	20,030 (5.3)	20,898 (5.1)
2010	25,293 (7.1)	18,745 (4.1)	20,045 (5.3)	21,258 (5.2)
2011	24,436 (6.8)	18,484 (4.1)	20,523 (5.5)	20,992 (5.1)
2012	23,949 (6.7)	18,447 (4.1)	20,216 (5.4)	21,007 (5.1)
2013	23,887 (6.7)	18,029 (4.0)	20,498 (5.5)	20,425 (5.0)
2014	24,119 (6.7)	18,436 (4.1)	19,945 (5.3)	20,752 (5.1)
2015	23,822 (6.7)	18,673 (4.1)	19,897 (5.3)	20,911 (5.1)
2016	24,131 (6.7)	18,597 (4.1)	20,212 (5.4)	20,858 (5.1)
2017	23,577 (6.6)	18,535 (4.1)	19,833 (5.3)	20,639 (5.1)
2018	21,670 (6.1)	17,790 (3.9)	19,774 (5.3)	19,777 (4.8)
2019	-	17,281 (3.8)	19,156 (5.1)	19,175 (4.7)
Person-years	1,438,699	2,824,641	1,861,501	2,112,841
Incidence	83,204 (23.3)	37,283 (8.2)	7,470 (2.0)	23,197 (5.7)
Incidence per year	(5.78)	(1.32)	(0.40)	(1.10)
Censored				
Becoming too old for study population	166,265	180,839	211,298	117,050
Moved outside study area	29,726	29,409	20,530	28,387
Moved to institute	409	843	772	670
Deceased	221	230	188	267

Table 5.8 Characteristics at baseline of the study populations for medication for asthma/COPD (0-5 years and 6-19 years), for depression (12-19 years) and for ADHD (6-14 years).

Individual Covariates	**asthma/ COPD *0-5 year* N (%)**	**asthma/ COPD 6-19 years N (%)**	**depression 12-19 years N (%)**	**ADHD 6-14 years N (%)**
Study population	357,793	454,630	374,878	408,391
Gender				
Males	181,481 (50.7)	229,976 (50.6)	192,552 (51.4)	207,939 (50.9)
Females	176,312 (49.3)	224,654 (49.4)	182,326 (48.6)	200,452 (49.1)
Age				
0	278,570 (77.9)			
1	18,380 (5.1)			
2	13,402 (3.8)			
3	14,877 (4.2)			
4	15,672 (4.4)			
5	16,892 (4.7)			
6		219,763 (48.3)		247,700 (60.7)
7		18,983 (4.2)		21,210 (5.2)
8		18,891 (4.2)		20,627 (5.1)
9		18,865 (4.2)		20,614 (5.1)
10		18,278 (4.0)		19,924 (4.9)
11		18,043 (4.0)		19,649 (4.8)
12		17,540 (3.9)	239,677 (63.9)	19,105 (4.7)
13		18,312 (4.0)	20,261 (5.4)	19,754 (4.8)
14		18,402 (4.1)	20,264 (5.4)	19,808 (4.8)
15		18,972 (4.2)	20,691 (5.5)	
16		19,028 (4.2)	20,650 (5.5)	
17		18,772 (4.1)	20,388 (5.4)	
18		16,489 (3.6)	17,735 (4.7)	
19		14,292 (3.1)	15,212 (4.1)	
Migration background				
Dutch	219,992 (61.5)	292,961 (64.4)	244,402 (65.2)	259,311 (63.5)
Netherlands Antilles	3,456 (1.0)	4,674 (1.0)	3,963 (1.1)	4,028 (1.0)
Suriname	12,522 (3.5)	22,572 (5.0)	20,182 (5.4)	19,044 (4.7)
Turkey	14,132 (4.0)	21,915 (4.8)	19,048 (5.1)	19,856 (4.9)
Morocco	25,902 (7.2)	34,485 (7.6)	28,976 (7.7)	33,356 (8.2)
Other, western	41,559 (11.6)	38,910(8.6)	28,961 (7.7)	35,498 (8.7)
Other, non-western	40,230 (11.3)	39,113 (8.6)	29,346 (7.8)	37,298 (9.1)

Table 5.8 Characteristics at baseline of the study populations for medication for asthma/COPD(0-5 years and 6-19 years), for depression (12-19 years) and for ADHD (6-14 years), continued.

Individual Covariates	asthma/ COPD *0-5 year* N (%)	asthma/ COPD 6-19 years N (%)	depression 12-19 years N (%)	ADHD 6-14 years N (%)
Household income				
≤ 1 percentile	4,485 (1.3)	5,009 (1.1)	3,409 (0.9)	3,760 (0.9)
>1-5 percentile	17,137 (4.8)	18,714 (4.1)	12,356 (3.3)	18,364 (4.5)
>5-10 percentile	17.761 (5.0)	24,125 (5.3)	19,501 (5.2)	23,910 (5.8)
>10-25 percentile	51,567 (14.4)	66,523 (14.6)	57,138 (15.2)	59,958 (14.7)
>25-50 percentile	88,849 (24.8)	114,294 (25.1)	93,025 (24.8)	103,369 (25.3)
>50-75 percentile	88,222 (24.7)	109,293 (24.0)	95,500 (25.5)	97,917 (24.0)
>75-90 percentile	51,151 (14.3)	69,779 (15.4)	58,223 (15.5)	58,574 (14.3)
>90-95 percentile	18,727 (5.2)	22,202 (4.9)	17,371 (4.6)	19,847 (4.9)
>95-99 percentile	15,829 (4.4)	18,866 (4.2)	14,111 (3.8)	17,394 (4.3)
>99 percentile	4,065 (1.1)	5,825 (1.3)	4,244 (1.1)	5,298 (1.3)

5.3.2 *Exposure*

The exposure distribution of the annual average concentrations of UFP from aviation for the 11 study populations is given in Table 5.9.

The 1-percentile of the annual average UFP distribution in the various medication cohorts has a 1-percentile of about 635 and a 99-percentile of 6,500 #/cm^3.

Since there are 11 cohorts and the exposure distributions are similar, we only provide information for the largest cohort about the exposure levels of the co-pollutants in Table 5.10 and about their correlations in Table 5.11.

Table 5.9 Distribution of annual average concentrations of UFP from aviation in the various medication cohorts in #/cm^3.

	N	Mean	SD	P1	P5	P10	P25	P50	P75	P90	P95	P99
heart disease 40 years and older	9,621,031	1,920	1,211	633	757	887	1,157	1,561	2,280	3,420	4,448	6,525
Parkinson's disease 40 years and older	9,229,895	1,907	1,210	633	754	881	1,146	1,547	2,258	3,397	4,427	6,551
dementia syndromes 40 years and older	9,262,348	1,906	1,209	633	754	881	1,146	1,546	2,257	3,397	4,427	6,549
asthma/COPD 20 years and older	11,899,027	1,911	1,198	635	758	887	1,156	1,557	2,265	3,396	4,411	6,457
hypertension 20 years and older	10,255,095	1,907	1,192	635	757	886	1,156	1,555	2,256	3,387	4,407	6,406
diabetes 20 years and older	13,513,773	1,912	1,201	633	755	884	1,155	1,557	2,269	3,402	4,418	6,465
depression 20 years and older	12,705,018	1,911	1,205	634	756	883	1,151	1,553	2,265	3,411	4,433	6,484
asthma/COPD 0-5 year	1,438,699	1,933	1,168	639	771	899	1,163	1,589	2,347	3,415	4,351	6,136
asthma/COPD 6-19 years	2,824,641	1,958	1,248	636	761	887	1,138	1,571	2,376	3,579	4,559	6,523
depression 12-19 years	1,861,501	1,960	1,263	633	756	882	1,135	1,567	2,372	3,609	4,605	6,584
ADHD 6-14 years	2,112,841	1,958	1,237	637	763	889	1,139	1,576	2,389	3,565	4,534	6,439

Table 5.10 Distribution of annual average concentrations of other air pollutants, and noise in the cohort for diabetes among 20 years and older.

	Mean	SD	P1	P5	P10	P25	P50	P75	P90	P95	P99
PM2.5	13.83	2.13	10.34	10.83	11.22	12.05	13.63	15.42	16.76	17.50	19.11
NO2	25,37	4.83	15.70	17.71	19.12	21.97	25.16	28.55	31.74	33.76	36.91
EC	1.01	0.27	0.61	0.68	0.72	0.80	0.96	1.15	1.37	1.53	1.80
PM25-EC	12.82	1.90	9.63	10.08	10.42	11.24	12.67	14.26	15.45	16.02	17.37
Aviation (24-hour) noise	53.13	0.76	53.00	53.00	53.00	53.00	53.00	53.00	53.00	53.00	57.30
Aviation night-time noise	43.08	0.58	43.00	43.00	43.00	43.00	43.00	43.00	43.00	43.00	45.90
Road traffic noise	55.80	4.12	53.00	53.00	53.00	53.00	53.00	57.70	62.20	64.70	69.10
Rail traffic noise	53.17	1.09	53.00	53.00	53.00	53.00	53.00	53.00	53.00	53.00	58.90

N=13,513,773, other air pollutants in µg/m^3, noise (L_{den} and L_{night}) in dB.

Table 5.11 Spearman's correlations between UFP from aviation, other air pollutants, noise, and indicators for neighbourhood SES in the cohort for diabetes among 20 years and older.

	PM2.5	NO_2	EC	PM2.5- EC	Aviation 24-h	Aviation night	Road traffic	Rail traffic	Income	High edu.	% non-western
UFP-aviation	-0.14	-0.00	-0.04	-0.15	0.19	0.08	0.05	-0.08	0.11	0.06	0.07
PM2.5	1.00	0.82	0.86	1.00	-0.07	-0.05	0.15	0.05	0.05	0.06	0.12
NO_2		1.00	0.95	0.79	-0.06	-0.07	0.33	0.08	0.06	0.28	0.35
EC			1.00	0.82	-0.08	-0.08	0.30	0.09	0.07	0.26	0.34
PM2.5-EC				1.00	-0.06	-0.05	0.13	0.04	0.04	0.04	0.09
Aviation (24-h) noise					1.00	0.61	-0.04	-0.01	0.03	-0.10	-0.13
Aviation (night) noise						1.00	-0.04	0.00	-0.01	-0.11	-0.13
Road traffic noise							1.00	0.08	0.04	0.18	0.13
Rail traffic noise								1.00	0.02	0.11	0.06
Mean income (rank)									1.00	0.69	-0.50
% High education										1.00	-0.08

N=13,513,773.

5.3.3 Associations between UFP from aviation and primary outcomes

5.3.3.1 Main model

We present the main results per type of effect: the respiratory, the cardiovascular combined with the metabolic, the nervous system and lastly psychological complaints.

Respiratory endpoints

The observed associations between UFP from aviation in all three age groups and for men and women are not an indication for a relation with the first-time dispension of medication for Asthma/COPD (Table 5.12).

Table 5.12 Result of the main model for first-time dispension of medication for respiratory disease for various age groups in relation to UFP in the calendar year of medication use (including marital status, migration background, household income, area level covariates, frailty).

Medication group	**Age group**	**Gender**	**HR per 3,500 #/cm^3**	**95%CI**
Asthma/COPD	0-5 years	Female	0.943	(0.873-1.018)
		Male	0.996	(0.927-1.071)
	6-19 years	Female	1.011	(0.927-1.104)
		Male	0.962	(0.881-1.049)
	20 years and older	Female	0.970	(0.924-1.018)
		Male	1.000	(0.950-1.053)

The inclusion of a frailty term in the sequence of statistical models with an increasing level of control for confounders led to larger confidence intervals as was foreseen. Adjustment of individual and neighbourhood SES had smaller effects on the effect estimates for men than for women in the age groups 0-5 and 6-19 year old. Increasing adjustment led to 95% confidence intervals that include a HR of 1 (Figure 5.1).

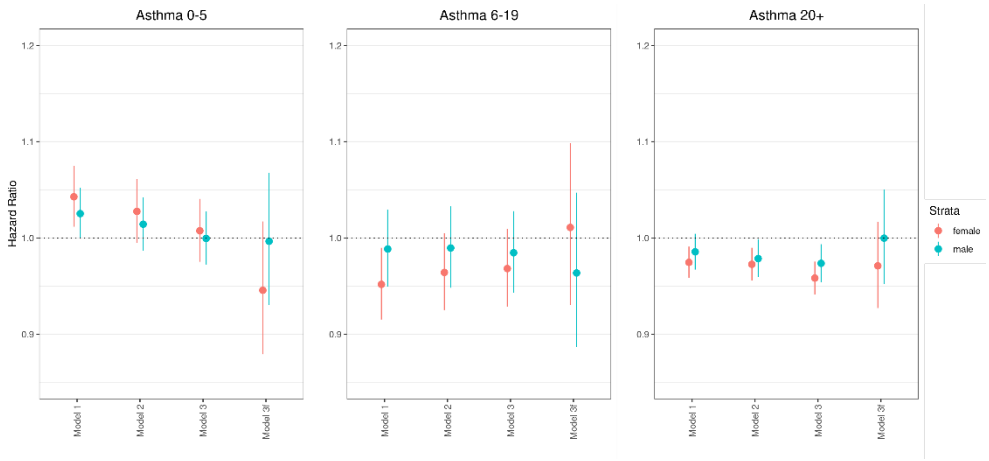


Figure 5.1 Associations between UFP from aviation and the incidence of Asthma/COPD among females and males of 0-5, 6-19 and 20 years and older. Hazard ratios (95% confidence intervals) presented for 3,500 #/cm3 increase in UFP. Model 1 included age (as the timescale) and three year periods of calendar years (strata); model 2 further adjusted for marital status, migration background, and household income; model 3 added neighbourhood-level income, percentage of inhabitants with non-western migration background, percentage of inhabitants with high education and model 3f included shared frailty.

We evaluated the influence of different exposure windows on the HR's (Figure 5.2). For the age group 0-5 years old we limited the comparison to the exposure during the calendar year under study and the exposure of the current and previous calendar year since newborns are part of this cohort.

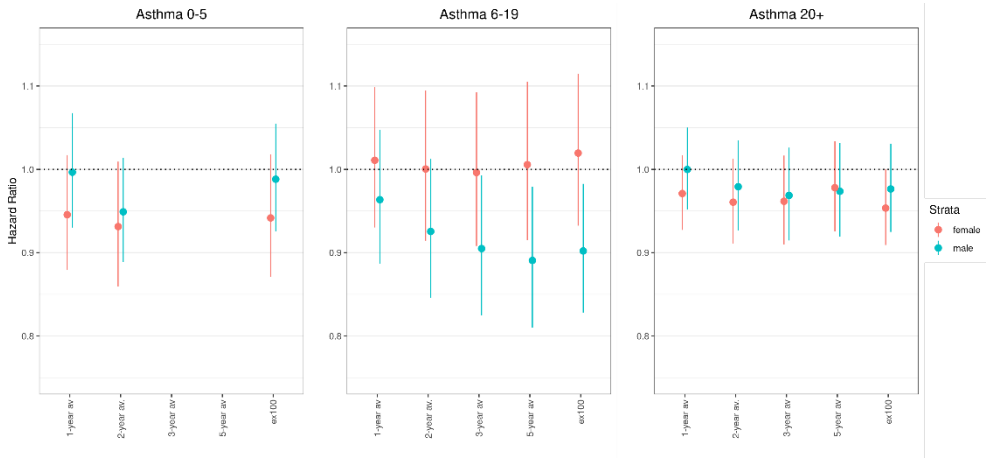


Figure 5.2 Associations between UFP from aviation and the incidence of Asthma/COPD among females and males of 0-5, 6-19 and 20 years and older for different exposure windows. Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,500 #/cm^3 increase in UFP or per 100 hours for concentrations above 66,667 #/cm^3 (ex100).

Using 2-, 3- and 5-years moving averages instead of an 1-year average did not have substantial effects on the associations with UFP in the age group 20 years or older and among females in the age group 6-19 years

old. For males in the latter age group, the HR's decreased when the exposure window was expanded. No differences were observed for the youngest cohort. Expressing the exposure as hours above 67,667 #/cm^3 did not change the HR's substantially.

Cardiovascular and metabolic endpoints
We found no statistical significant associations for the medication groups for heart disease, for hypertension and for diabetes, except for the dispension of medication for heart disease among men (HR=1.041 per 3,500 #/cm^3) (Table 5.13). The incidence of medication for heart disease among women was not elevated.

Table 5.13 Result main model for first-time dispension of medication for cardiovascular and metabolic disorders in relation to UFP in the calendar year of medication use (including marital status, migration background, household income, area level covariates, frailty).

Medication group	**Age group**	**Gender**	**HR per 3,500 #/cm^3**	**95%CI**
Heart disease	40 years and older	Female	1.003	(0.961-1.048)
		Male	1.041	(1.003-1.081)
Hypertension	20 years and older	Female	1.000	(0.968-1.034)
		Male	1.003	(0.975-1.032)
Diabetes	20 years and older	Female	0.970	(0.922-1.021)
		Male	1.012	(0.965-1.060)

The adjustment of individual and neighbourhood SES and inclusion of a frailty term led to an increase of the HR per 3,500 #/cm^3 for heart disease among male, but did not affect the HR for females substantially (Figure 5.3). We observed no effects on the HR's for hypertension, while for diabetes increasing adjustment led to 95% confidence intervals that include a HR of 1.

The exposure estimates for cardiovascular and metabolic disorders did not change when 2-, 3- or 5-years moving averages or the hours above 66,667 #/cm^3 were applied instead of a 1-year average (Figure 5.4).

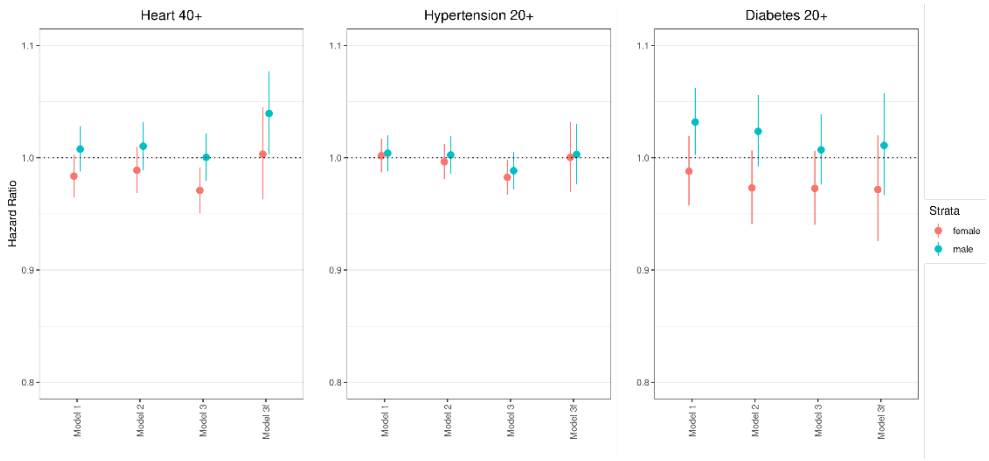


Figure 5.3 Associations between UFP from aviation and the incidence of cardiovascular and metabolic disorders among females and males of 20 or 40 years and older. Hazard ratios (95% confidence intervals) presented for 3,500 #/cm^3 increase in UFP. Model 1 included age (as the timescale) and three year periods of calendar years (strata); model 2 further adjusted for marital status, migration background, and household income; model 3 added neighbourhood-level income, percentage of inhabitants with non-western migration background, percentage of inhabitants with high education and model 3f included shared frailty.

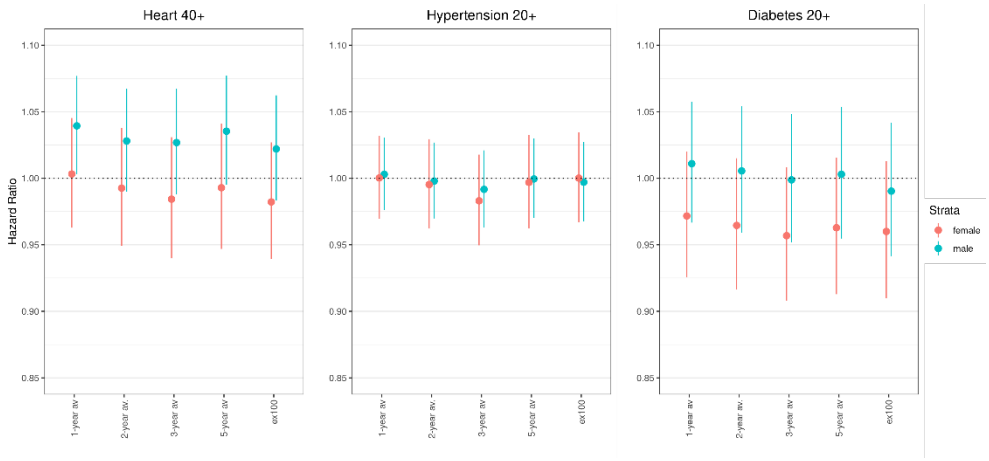


Figure 5.4 Associations between UFP from aviation and the incidence of cardiovascular and metabolic disorders among females and males of 20 or 40 years and older. Hazard ratios (95% confidence intervals) presented for 5000 #/cm^3 increase in UFP. for different exposure windows. Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,500 #/cm^3 increase in UFP or per 100 hours for concentrations above 66,667 #/cm^3 (ex100).

Neurodegenerative outcomes

The results for the medication groups for Parkinson's disease and for dementia syndromes have relative large confidence intervals due to the low incidence (Table 5.14). The HR for the dispension of medication for dementia syndromes, a secondary endpoint, among women was increased (HR=1.236 per 3,500 #/cm^3); the increase of the HR (1.057) among men was not statistically significant.

Table 5.14 Result main model for first-time dispension of medication for neurodegenerative diseases in relation to UFP in the calendar year of medication use (including marital status, migration background, household income, area level covariates, frailty).

Medication group	Age group	Gender	HR per 3,500 #/cm^3	95%CI
Parkinson's disease	40 years and older	Female	0.972	(0,868-1.090)
		Male	1.013	(0.937-1.097)
Dementia syndromes (secondary endpoint)	40 years and older	Female	1.236	(1.042-1.467)
		Male	1.057	(0.895-1.250)

Adjustment of individual and neighbourhood SES and inclusion of a frailty term had little effect on the HR's of UPF for the medication groups for Parkinson's disease and for dementia syndromes (Figure 5.5).

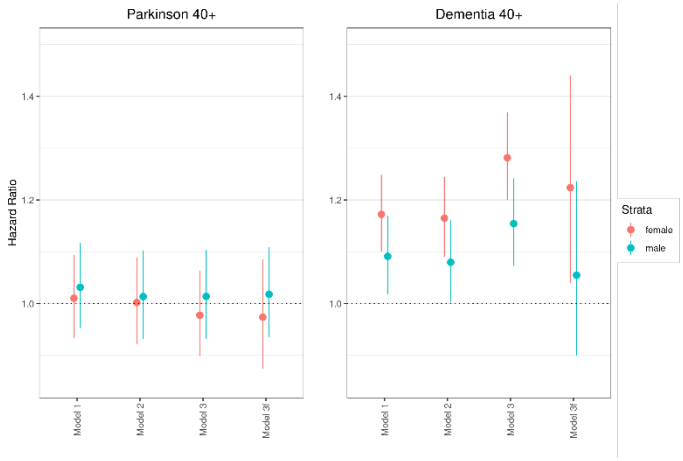


Figure 5.5 Associations between UFP from aviation and the incidence of neurodegenerative diseases among females and males of 40 years and older. Hazard ratios (95% confidence intervals) presented for 3,500 #/cm^3 increase in UFP. Model 1 included age (as the timescale) and three year periods of calendar years (strata); model 2 further adjusted for marital status, migration background, and household income; model 3 added neighbourhood-level income, percentage of inhabitants with non-western migration background, percentage of inhabitants with high education and model 3f included shared frailty, except for Parkinson's disease among men (robust standard errors).

Using 2-, 3- and 5-years moving averages led to a decreasing HR's for medication for Dementia syndromes among women leading to HR's that were no longer statistically significant (Figure 5.6). The hours above 66,667 #/cm^3 instead of a 1-year average did affect the HR for Dementia syndromes among men leading to an elevated HR.

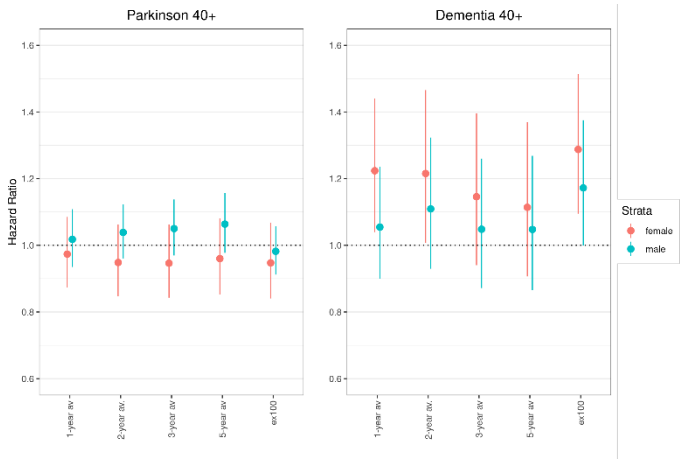


Figure 5.6 Associations between UFP from aviation and the incidence of neurodegenerative diseases among females and males of 40 years and older for different exposure windows. Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,333 #/cm^3 increase in UFP or per 100 hours for concentrations above 66,667 #/cm3 (ex100).

Psychological complaints
The use of anti-depressants and ADHD are all secondary outcomes.

In general there is a negative association between UFP and the incidence of these medication groups (Table 5.15). Dispension of anti-depressants among 12-19 years old and of ADHD among females are statistically significant.

Table 5.15 Result main model for first-time dispension of medication related to psychological complaints in relation to UFP in the calendar year of medication use (including marital status, migration background, household income, area level covariates, frailty).

Medication group	Age group	Gender	HR per 3,500 #/cm^3	95%CI
Anti-depressants (secondary endpoint)	20 years and older	Female	0.993	(0.954-1.033)
		Male	0.993	(0.946-1.043)
	12-19 years	Female	0.826	(0.726-0.939)
		Male	0.769	(0.661-0.895)
ADHD (secondary endpoint)	6-14 years	Female	0.800	(0.684-0.937)
		Male	0.912	(0.826-1.008)

The adjustment of individual and neighbourhood SES and inclusion of a frailty term had little influence on the size of the HR's (Figure 5.7), but the adjustment led to a statistical non-significant HR for the medication for ADHD among males.

The exposure estimates did not change substantially when 2-, 3- or 5-years moving averages were applied instead of a 1-year average (Figure 5.8).

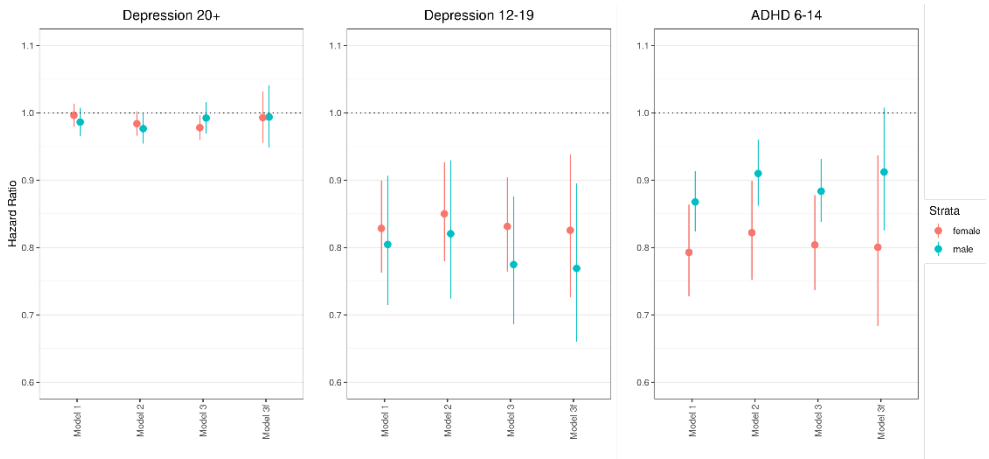


Figure 5.7 Associations between UFP from aviation and the incidence of anti-depressants among 20 years and older and 12-19 year olds and medication for ADHD of 6-14 year olds. Hazard ratios (95% confidence intervals) presented for 3,500 #/cm^3 increase in UFP. Model 1 included age (as the timescale) and three year periods of calendar years (strata); model 2 further adjusted for marital status, migration background, and household income; model 3 added neighbourhood-level income, percentage of inhabitants with non-western migration background, percentage of inhabitants with high education and model 3f included shared frailty.

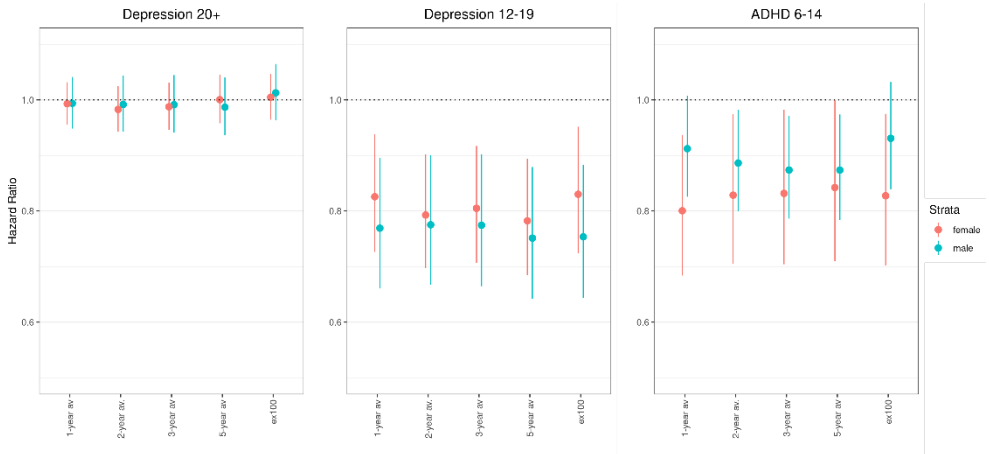


Figure 5.8 Associations between UFP from aviation and the incidence of anti-depressants among 20 years and older and 12-19 year olds and medication for ADHD of 6-14 year olds for different exposure windows. Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,500 #/cm^3 increase in UFP or per 100 hours for concentrations above 66,667 #/cm^3 (ex100).

5.3.3.2 Spline plots

With a Cox model with regression splines on UFP (simply referred later as the spline Cox model) we explored whether the annual average UFP concentrations reveals non-linear effects on the incidence of the various medication groups. The resulting spline plots are presented per type of effect: the respiratory (Figure 5.9), the cardiovascular combined with the metabolic (Figure 5.10) and the nervous system (Figure 5.11) and lastly the psychological complaints (Figure 5.12).

It can be seen from the Figures 5.9 to 5.12 that in all medication cohorts the non-linear effect is in agreement with the estimated linear effect for the vast majority of outcomes (see Tables 5.12-5.15) over the exposure range from 650 to 10,000 #/cm^3. Exposure distributions are included in the plots. A level of 10,000 #/cm^3 is exceeded on the home address of, on average, 0.04% of the population in the various cohorts. About 1,8% of the study populations has an annual average concentration lower than 650 #/cm^3. Overall, higher UFP values increase the estimation uncertainty.

The behaviour of the non-linear effects in the left and right tail (below 650 and above 10,000 #/cm^3) is shown in Appendix 5 (Figures A.5.1 to A.5.4). The behaviour is very uncertain due to the small number of events in the tails of the UFP exposure distribution.

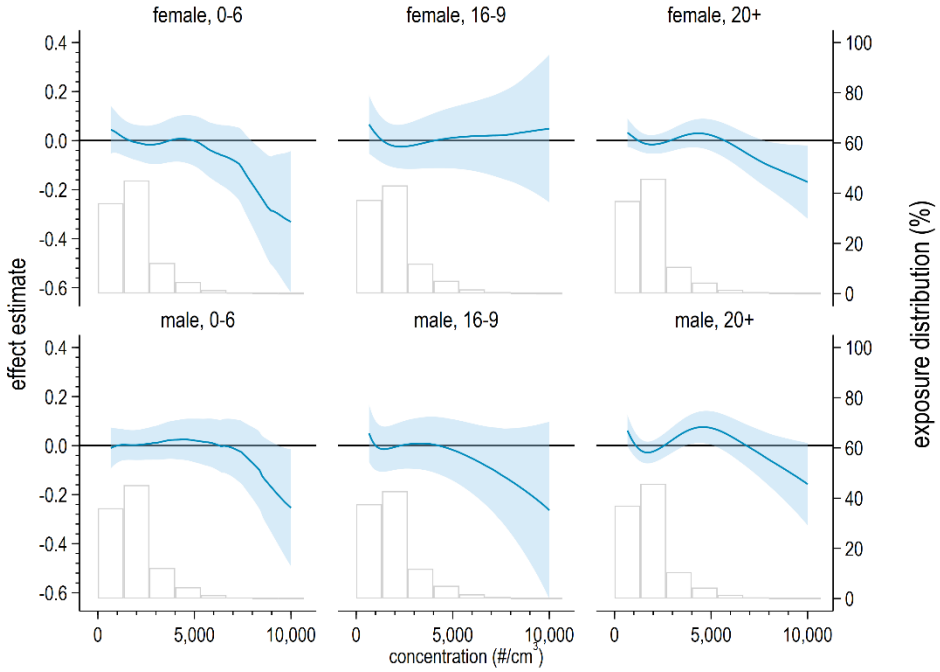


Figure 5.9 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of Asthma/COPD among females and males of 0-5, 6-19 and 20 years and older. Blue area: 95% confidence intervals. Exposure range limited to 650-10,000 #/cm^3.

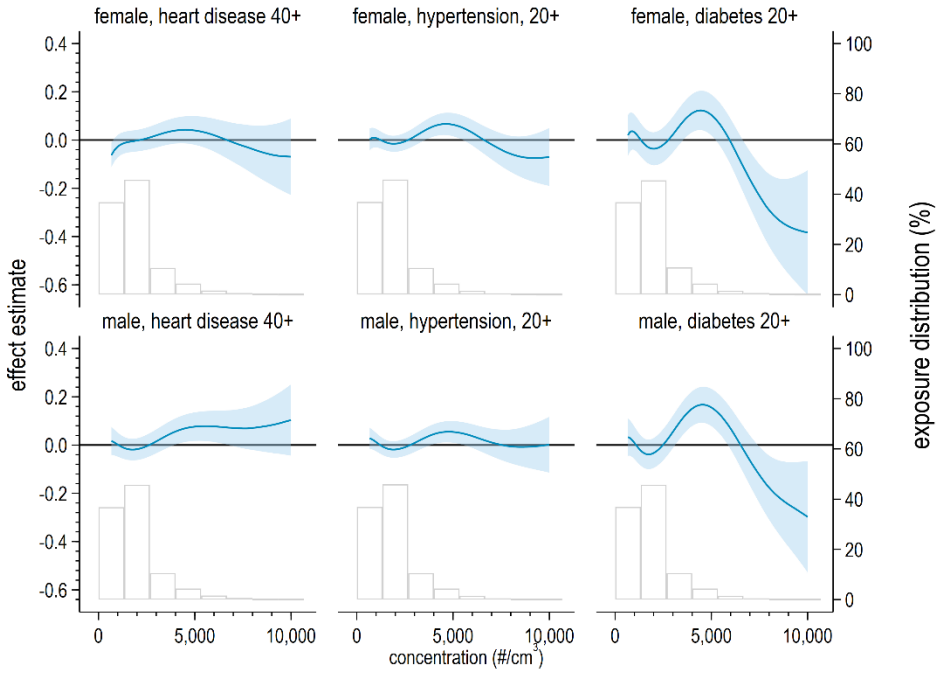


Figure 5.10 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of cardiovascular and metabolic disorders among females and males of 20 or 40 years and older. Blue area: 95% confidence intervals. Exposure range limited to 650-10,000 #/cm³.

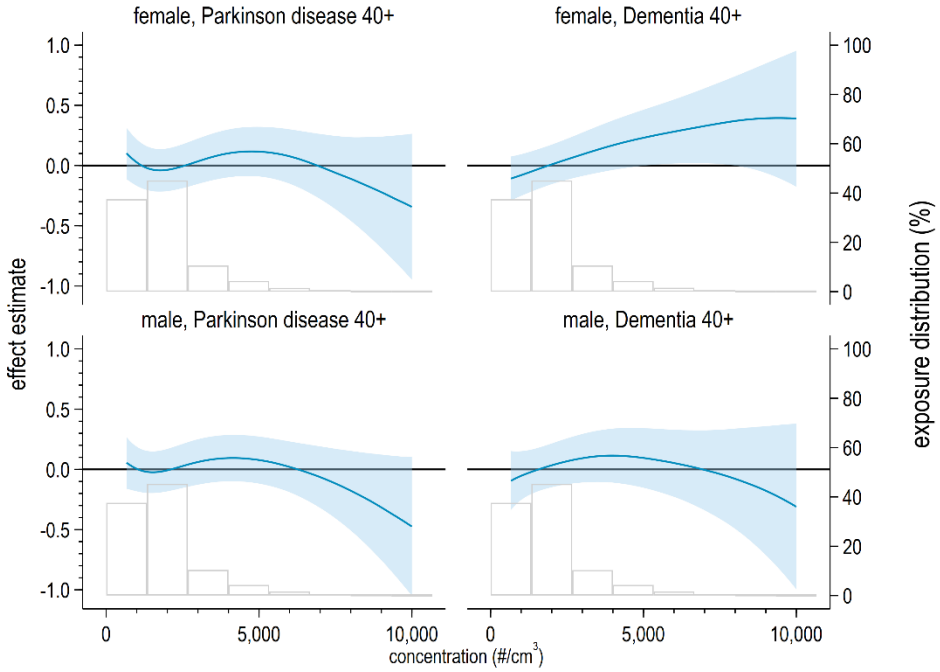


Figure 5.11 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of neurodegenerative diseases among females and males of 40 years and older. Blue area: 95% confidence intervals. Exposure range limited to 650-10,000 #/cm³.

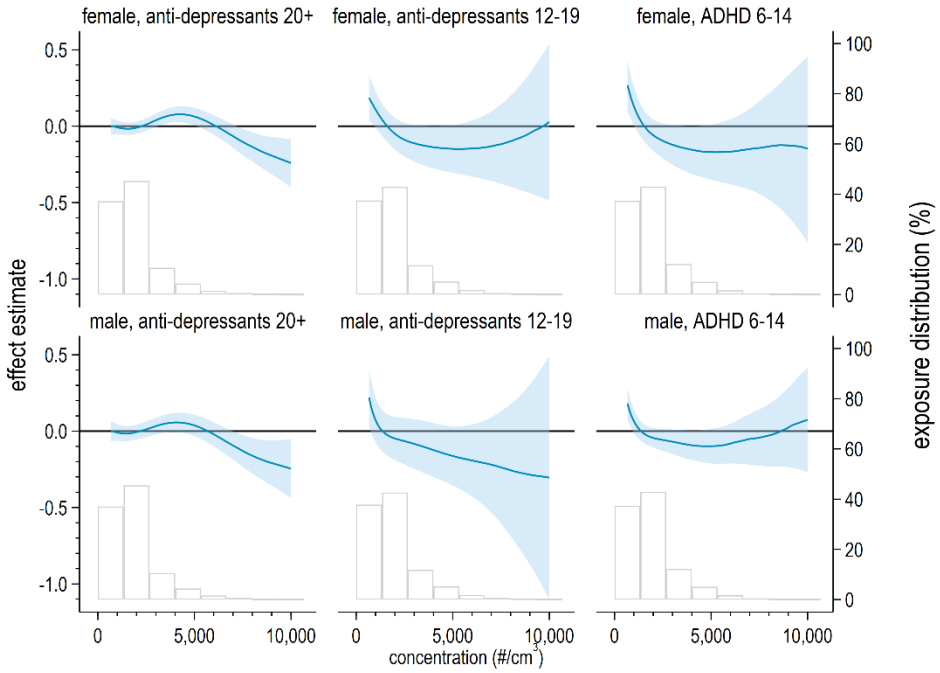


Figure 5.12 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of anti-depressants among 20 years and older and 12-19 years olds and medication for ADHD of 6-14 years olds. Blue area: 95% confidence intervals. Exposure range limited to 650-10,000 #/cm^3.

5.3.3.3 Sensitivity analyses and stratifications

The results of the sensitivity analyses and stratifications are again presented per organ system in the figures 5.13 to 5.16.

In the sensitivity analyses the HR of UFP for medication for heart disease among men was relatively robust (Figure 5.14). It slightly decreased after adjustment for NO_2 or EC and was somewhat lower in areas with a relative low urbanicity; the 95% confidence intervals included a HR of 1.

The raised effect estimate for medication for dementia syndromes among women was not affected in the multipollutant and stratified analyses (Figure 5.15).

The lower HR's of UFP for anti-depressants and medication for ADHD in the young age groups did not change substantially in the multi-pollutant models (Figure 5.16). The magnitude of the HR's and their statistical significant were somewhat sensitive for the stratification for urbanicity and when the four municipalities with the lowest exposure were excluded.

The HR's of UFP from the larger cohorts consisting of participants of 20 years and older (medication for asthma/COPD, for hypertension, for diabetes and for depression) were in general robust in the sensitivity analyses.

The multi-pollutant models did not affect the results with the exception of the adjustment for PM2.5 and NO2 in the medication group of

Asthma/COPD for the age groups 0-5 and 20 years and older (Figure 5.13). The directions were different: among children 0-5 years old the effect estimates decreased and the HR for females became lower than unity and statistically significant. For the older group the HR's increased slightly.

In most cohorts, the stratification for urbanisation had some effect on the HR's of UFP, which was most visible in the smaller cohorts (0-5, 6-12, 12-19 and 6-19 years old). The changes were not consistent across cohorts. For example, for Asthma/COPD in the age group 0-5 years the HR's in rural areas were slightly higher than in urban areas, while the opposite effect occurred in the age group 6-19 years old (Figure 5.13). The HR of UFP for heart disease among women increased in areas with higher urbanicity; an opposite effect is seen for medication for diabetes (Figure 5.14). In areas with a lower address density, the HR of UFP for Parkinson's disease among women decreased, while the change in effect size among men was small and in the opposite direction (Figure 5.15). For medication for Dementia syndromes among men, the change in HR was more visible leading to an elevated HR with similar size to the one for women in areas with high urbanicity.

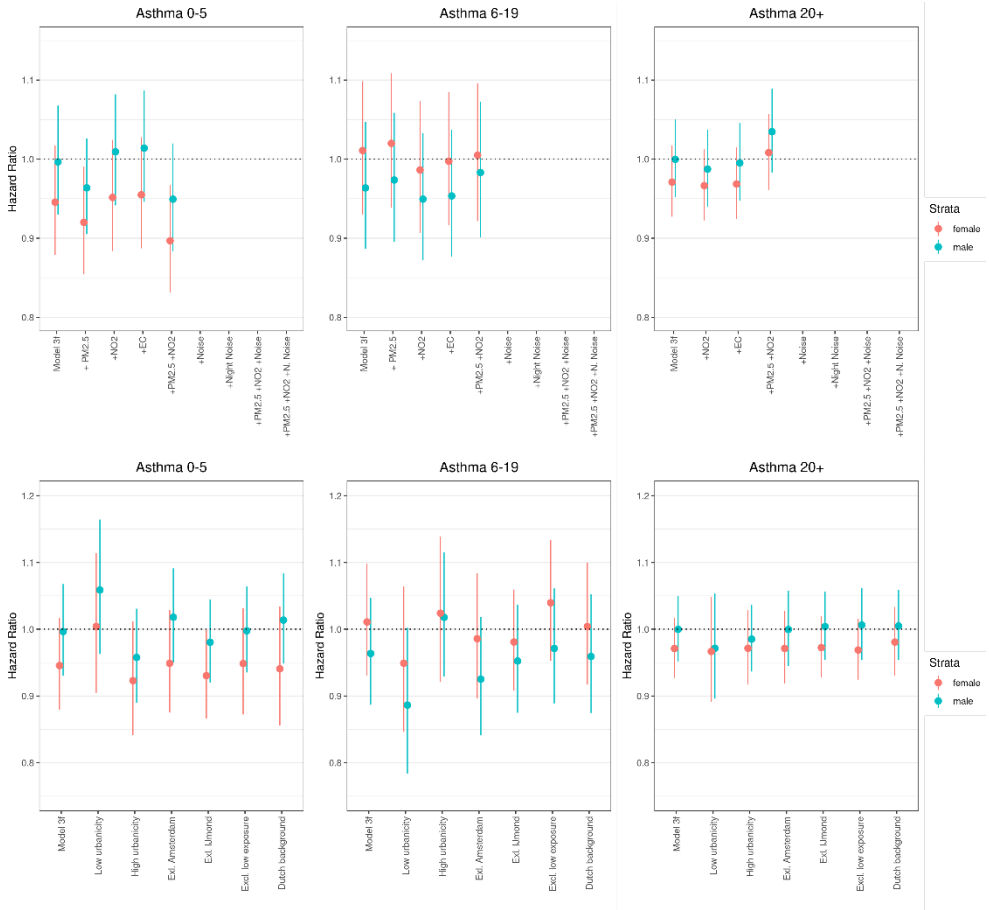


Figure 5.13 Associations between UFP from aviation and the incidence of Asthma/COPD among females and males of 0-5, 6-19 and 20 years and older in multipollutant models (above) and in sensitivity analyses (below). Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,500 #/cm^3 increase in UFP.

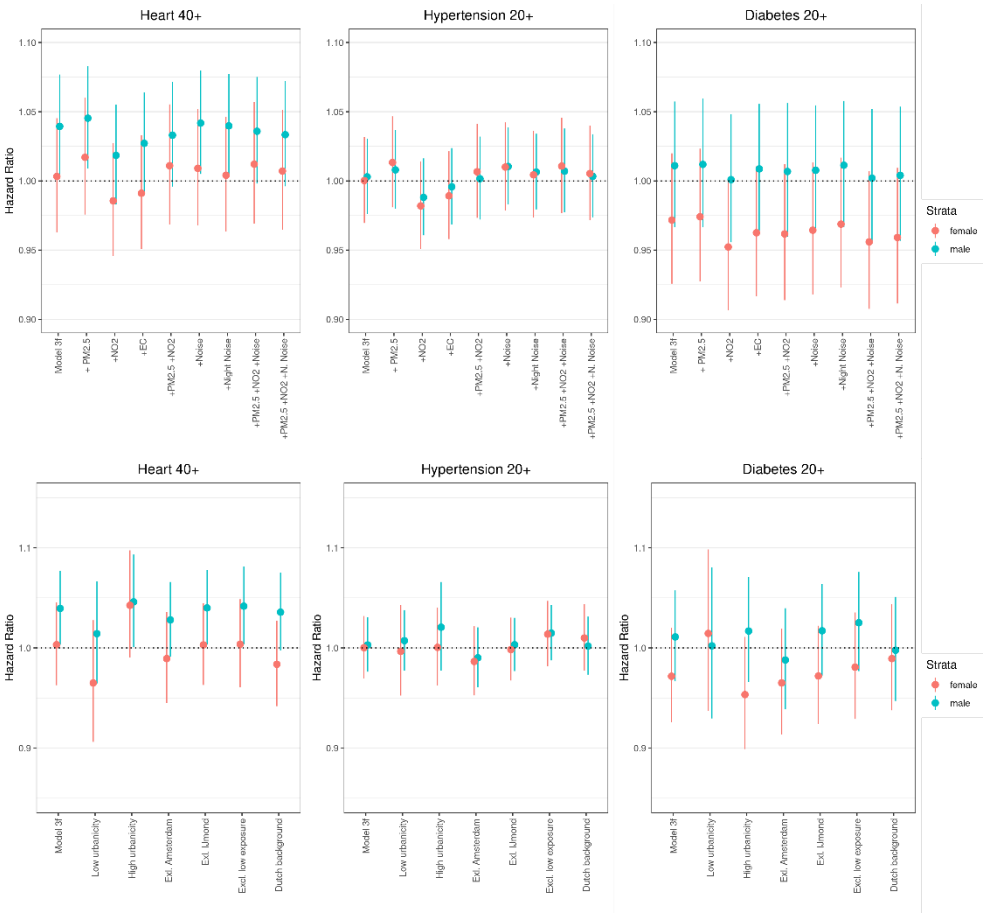


Figure 5.14 Associations between UFP from aviation and the incidence of cardiovascular and metabolic disorders among females and males of 20 or 40 years and older in multipollutant models (above) and in sensitivity analyses (below). Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,500 #/cm^3 increase in UFP.

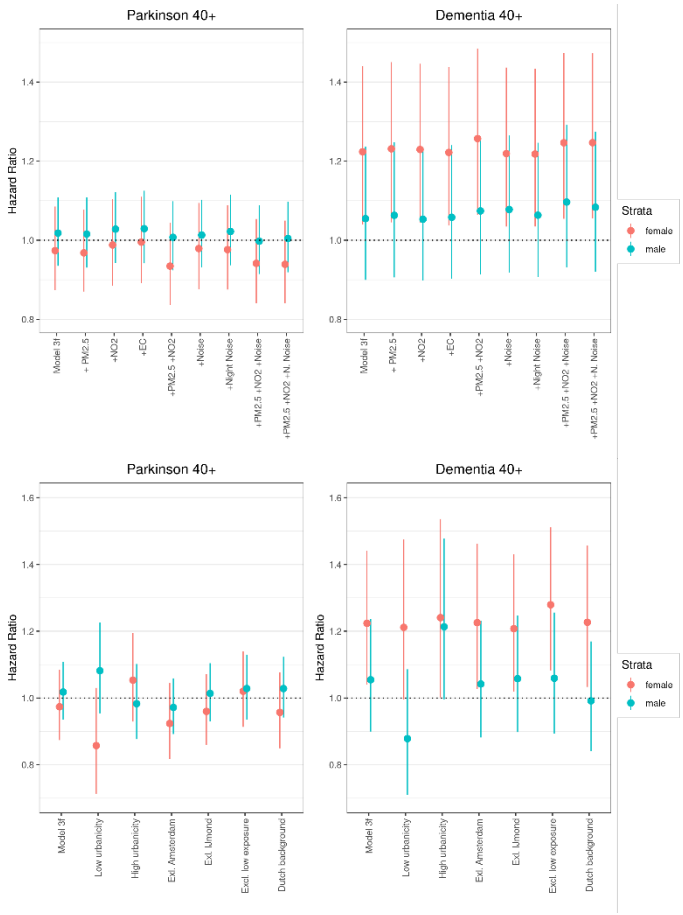


Figure 5.15 Associations between UFP from aviation and the incidence of neurodegenerative diseases among females and males of 40 years and older in multipollutant models (above) and in sensitivity analyses (below). Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,500 #/cm^3 increase in UFP.

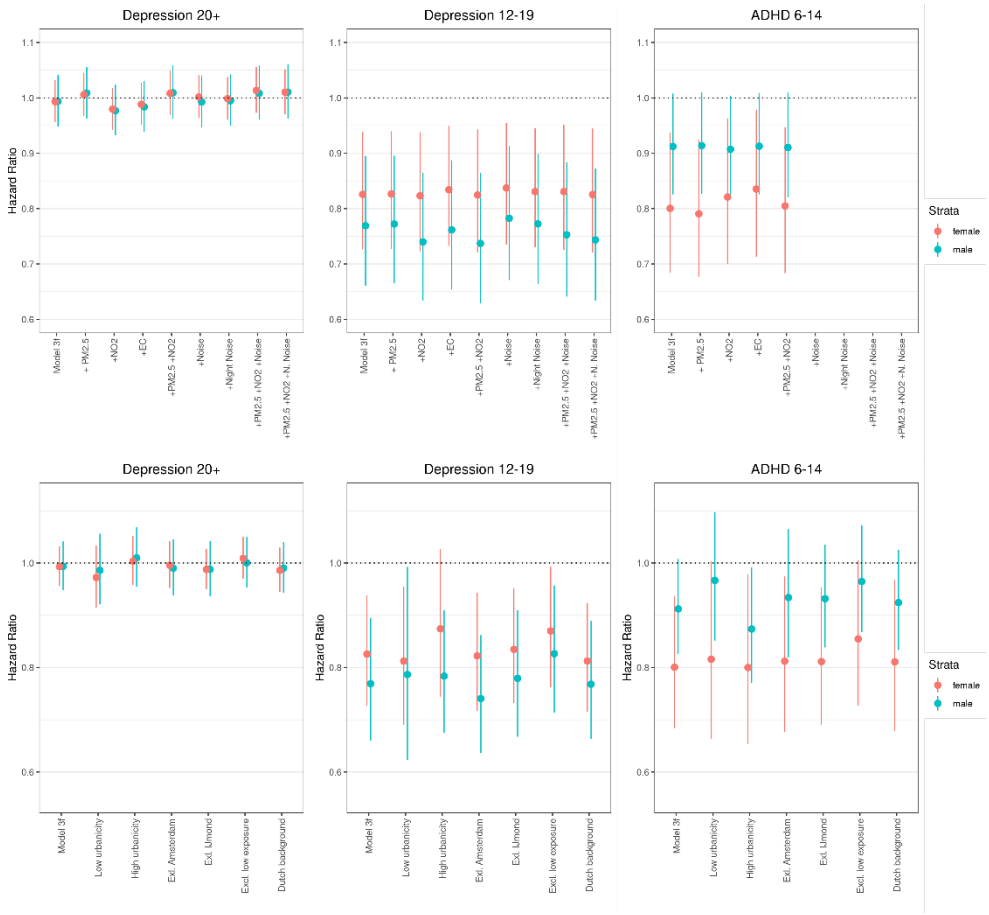


Figure 5.16 Associations between UFP from aviation and the incidence of anti-depressants among 20 years and older and 12-19 years olds and medication for ADHD of 6-14 years olds in multipollutant models (above) and in sensitivity analyses (below). Hazard ratios (95% confidence intervals) from the main linear model (model 3f) presented for 3,500 #/cm^3 increase in UFP.

5.4 Main findings

5.4.1 Summary and classification

Table 5.16 presents a summary of the results in the main model and the overall classification of the different outcomes, organized per type of effect. The last four rows (in italic) in the table concern the secondary outcomes (dementia, depression and ADHD).

The Hazard Rate is given separately for females and males. Additionally, a pooled estimate was calculated for easier comparison between the results of the medication study and the results from the other sub studies. A medium heterogeneity was seen for ADHD when the estimates of men and women were pooled. There was a small to medium heterogeneity for heart disease and dementia syndromes, a small heterogeneity for the estimates of diabetes and almost no heterogeneity for asthma, hypertension, Parkinson's disease and depression.

Table 5.16 Summary of results in the main model and classification of the association, per type of effect. HR per 3,500 #/cm³ (secondary outcomes in italics).

	Females		Males		Pooled		
Health outcome	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**Classification**
Respiratory							
Asthma/COPD (0-5 yrs)	0.943	(0.873-1.018)	0.996	(0.927-1.071)	0.971	(0.921-1.023)	No association
Asthma/COPD (6-19 yrs)	1.011	(0.927-1.104)	0.962	(0.881-1.049)	0.986	(0.927-1.049)	No association
Asthma/COPD (20+)	0.970	(0.924-1.018)	1.000	(0.950-1.053)	0.984	(0.950-1.019)	No association
Cardiovascular							
Heart disease (40+)	1.003	(0.961-1.04)	1.041	(1.003-1.081)	1.025	(0.997-1.054)	Probable association
Hypertension (20+)	1.000	(0.968-1.034)	1.003	(0.975-1.032)	1.002	(0.981-1.024)	No association
Metabolic							
Diabetes (20+)	0.970	(0.922-1.021)	1.012	(0.965-1.060)	0.992	(0.959-1.027)	No association
Neurodegenerative							
Parkinson's disease (40+)	0.972	(0.868-1.090)	1.013	(0.937-1.097)	1.000	(0.937-1.067)	No association
Dementia syndromes (40+)	*1.236*	*(1.042-1.467)*	*1.057*	*(0.895-1.250)*	*1.141*	*(1.013-1.286)*	*Clear association*
Psychological complaints							
Anti-depressants (20+)	*0.933*	*(0.954-1.033)*	*0.993*	*(0.946-1.043)*	*0.993*	*(0.963-1.024)*	*No association*
Anti-depressants (12-19 yrs)	*0.826*	*(0.726-0.939)*	*0.769*	*(0.661-0.895)*	*0.802*	*(0.727-0.884)*	*Inverse association*
ADHD (6-14 yrs)	*0.800*	*(0.684-0.937)*	*0.912*	*(0.826-1.008)*	*0.879*	*(0.808-0.956)*	*Inverse association*

5.4.2 Rationale for the classification

We found no associations between UFP from aviation and the incidence of medication use for the primary outcome **Asthma/COPD** in the main model. Therefore, the classification is "**no association**" for all three age groups. The spline Cox model confirms the results of the analyses with UFP as a linear exposure variable. In most subgraphs there is a slight decreasing trend in the effect estimate, but the confidence intervals are relatively large at UFP concentration above 7,000 #/cm3, related to the sparsity of exposed residents. For the age groups 0-5 and 20 years and older, the adjustments for PM2.5 and NO_2 had the largest influence on the effect estimates (Figure 5.13, upper graph). The directions of the effects were different: among children 0-5 years old the effect estimates decreased and the HR for females became statistically significantly lower than 1. For the older group, the HR's increased slightly. The HR's among females and males in the youngest age group were slightly higher in rural areas compared to urban areas, while in the age group 6-19 years old the effect was in opposite direction. The exclusion of Amsterdam had a no noteworthy impact on the effect estimates. In summary, the results of the co-pollutant or stratified analysis models did not indicate any clear deviations of the classification "no association".

We observed a "**probable association**" for the primary outcome **heart disease**; the pooled HR almost reached statistical significance (p=0.086). For men there was a gradual increase of the predicted estimate with rising UFP concentrations from aviation, confirming the results of the linear model (Figure 5.10). The size of the HR of UFP for men was robust in the sensitivity analyses, but the lower confidence interval fluctuated around a HR of 1. The HR's were slightly affected by the co-pollutants NO_2 and EC (Figure 5.14) and there was a slightly lower HR in areas with a relatively low urbanicity. The HR for heart disease among women increases in areas with higher urbanicity, but in general there was no association with UFP.

We observed **"no associations"** for medication for **hypertension, diabetes** and **Parkinson's disease**. The concentration-response curves had a similar pattern for these three primary health outcomes (a small decrease of the estimate followed by an increase up to effect estimates above 0, followed by a decline for UFP concentration above 7,000 #/cm^3). The pattern was the most pronounced for diabetes. In the sensitivity analyses, adjustment for the co-pollutants NO_2 and EC slightly affected the HR's of medication for hypertension; this was not seen for diabetes and Parkinson's disease. In areas with a lower address density, the HR for Parkinson's disease among women decreased while the effect among men is small and in the opposite direction. The classification "no association" was not disputed by the results of the various sensitivity analyses.

We classified the findings for **dementia syndromes**, a secondary endpoint, as a "**clear association"**. The pooled HR of 1.14 per 3,500 #/cm^3 was statistically significant (p=0.030). The result of the spline Cox model is in line with the results of the linear model. The HR for women was robust in sensitivity analyses, but decreased and lost statistical significance when the exposure window was prolonged from 1-year average to 3- and 5-years moving averages. Among men, the HR

was generally elevated, but did not reach statistical significance in the main model or in the sensitivity analyses.

We observed **"no association"** between UFP exposure and the incidence of **anti-depressants in the age group 20 years and older** (secondary outcome). This classification was supported by the spline plots and the results of the sensitivity analyses.

The incidence of **antidepressants** and medication for **ADHD** was **in the younger age groups "inversely associated"** with UFP from aviation (both secondary outcomes). These are biologically implausible associations.

The observed associations and their classification are further discussed in chapter 7 where conclusion are drawn per type of effect.

5.4.3 Study specific aspects

5.4.3.1 Introduction

In this paragraph, we describe specific characteristics of the medication study that may affect the quality of the results. For the general aspect, like the exposure assessment of UFP and the adjustment to co-pollutants, we refer to chapter 7.

5.4.3.2 Classification of the health outcomes

In this substudy we interpret the incidence of using a particular medication from the medication group under study as the onset of the treatment for a disease or disorder. However, we did not observe the onset directly, because no data from general practitioners or on hospital admissions were used.

We assume that for the primary endpoints there is sufficient similarity between the incidence of medication use and the onset of the treatment of the disorder. Slobbe et al. (2019) compared the prevalence of medication use with the diagnosis for chronic diseases in GP files for 29 chronic diseases. They applied a random forest algorithm; the agreement was measured with the Area Under the Curve (AUC). An AUC value above 0.7 is generally considered useful. The agreement was the highest for Parkinson's disease (AUC=89%). A good match was also found for diabetes (87%), heart failure (81%), COPD (79%) and asthma (77%). For coronary heart disease, the agreement was sufficient (70%). Although Slobbe et al. applied a much more detailed approach than was used in our sub study, we used the reported results to make a distinction between primary and secondary endpoints. The agreement for dementia (67%) and depressive disorder (58%) was less, so we therefore classified these outcomes as secondary endpoints at the start of the study.

Hypertension and ADHD were not included in the study by Slobbe et al. We included hypertension as a primary endpoint since in earlier studies around Schiphol airport pharmacy prescription data had been used for this endpoint (Knipschild and Oudshoorn, 1977; Houthuijs and van Wiechen, 2006). We selected ADHD since this pharmacy cost groups is related to the health endpoints under study. No information is known

about the prediction of medication use for an attention deficit hyperactivity disorder.

Mulder et al. (2016) carried out a validation study among Dutch children aged 0 to 10 years old. The sensitivity and positive predictive value (PPV) of various medication proxies for the identification of children diagnosed with asthma was computed using the registered diagnoses as gold standard. The proxy ≥1 prescription for anti-asthmatic drugs within 1 year detected 92% of the children with an asthma diagnosis. As consequence, 46% of the included cases were false positives. The detection was less in 0-5 years old (90%) than in 6-10 year old children (94%). Also, the percentage of false positives were higher among the youngest age group (52% versus 29%). Of the children that got prescribed anti-asthma drugs, 28% had a diagnosis of acute bronchitis and/or 24% a diagnosis of cough without a connected asthma diagnosis.

We cannot entirely rule out that the medication was already being used previously and that a registered event is actually a repeat prescription. The probability of a repeat prescription being issued after some time is likely the highest for Asthma/COPD. Therefore, for all medication groups, potential participants were only included in the study if they had not used any medication during the two-year period prior to the study. In doing so, we reduced the probability that a repeat prescription would be considered a first treatment of asthma or COPD.

5.4.3.3 Antidepressants and ADHD among children and adolescents

We observed inverse associations between UFP and the incidence of medication for ADHD among 6-14 year olds and for antidepressants among 12-19 years old. From a mechanistic view point, it is implausible to expect that there is a protective effect.

Further inspection of the results revealed that in the ADHD cohort among children and adolescents exposed at higher UFP levels (3,500 #/cm^3 and above), the event of medication dispensing was much more common among residents with Dutch citizenship with a high socioeconomic position. Besides, the incidence was extremely low, amounting to less than 10 events in 89% of the districts for the mix defined by gender, migration background and UFP levels. In the anti-depressant cohort, the pattern was similar, while the incidence was even less than for ADHD, namely 95% of districts present with less than 10 event for the mix defined by gender, migration background and UFP levels. Our statistical modelling approach may have led to the risk of UFP not being properly estimated in this specific situation of a low incidence and specific study participant profiles.

5.4.3.4 Strengths and limitations

We applied a longitudinal study design in which the incidence was followed over time in separate administrative cohorts per combination of medication and age group. A strong point is the size of the study population. This has been maximised by using population data sources that cover the entire study area and the 12 year study period. Subsequently, a more stringent study population was constructed by selecting from eligible participants only those who had lived in the same district for some time and excluding factors that could influence

exposure and medication use (such as moving or withdrawing from medication registration due to institutionalisation).

The exposure to UFP from aviation and co-pollutants and the demographic and socio-economic factors were used "time varying" by updating the exposure and covariates yearly over the entire study period. We evaluated different exposure windows for the exposure to UFP since we did not have prior knowledge about the possible critical exposure window. Also, we carried out several sensitivity analyses to assess the robustness of the main model.

An important limitation is that this substudy lacks information on individual lifestyle factors. This means that the magnitudes of the HRs may be biased if, for example, smoking is more prevalent among residents with a higher exposure to UFP emissions from aviation. We limited residual confounding by adjusting for an extensive set of both individual- and area-level SES indicators and by incorporating a Cox frailty model. The associations between exposure to UFP-aviation and lifestyle variables within the mortality cohort of 30 years or older (paragraph 6.3.6.3, table 6.9) showed that current smoking, alcohol consumption and low physical activity were associated with somewhat lower exposure to UFP from aviation, while overweight and obesity were associated with higher exposure to UFP from aviation. With the exception of overweight, none of these differences were statistically significant. These results suggest that potential bias in the medication cohorts among populations of 20 years or older and 40 years or older is limited.

5.5 Appendix

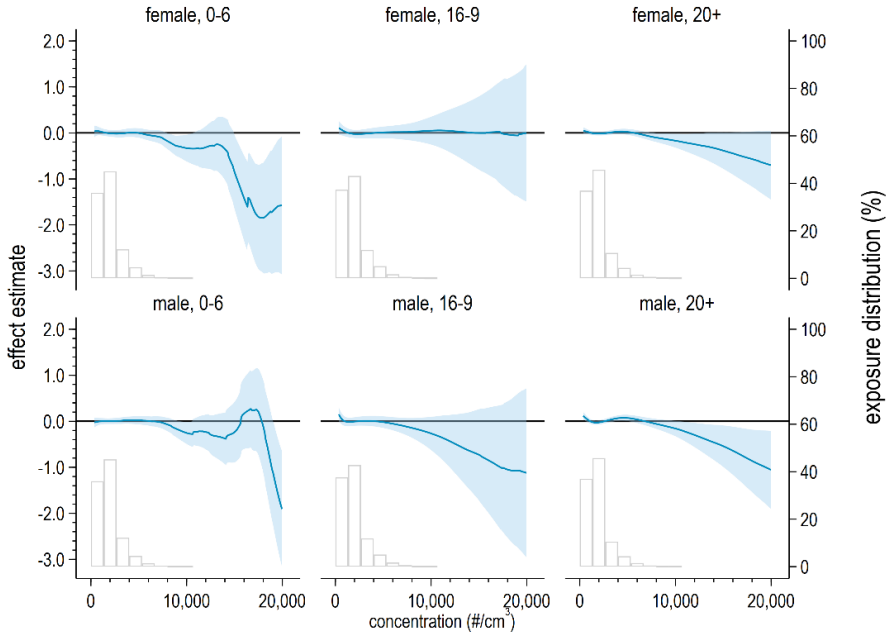


Figure A.5.1 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of Asthma/COPD among females and males of 0-5, 6-19 and 20 years and older. Blue area: 95% confidence intervals. Exposure range limited to 333-20,000 #/cm^3.

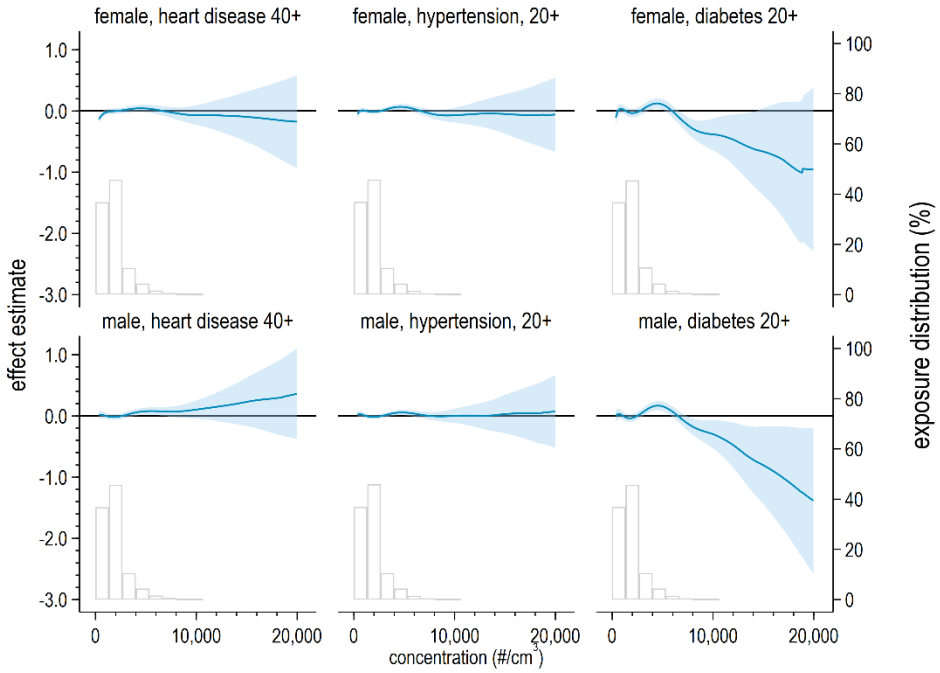


Figure A.5.2 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of cardiovascular and metabolic disorders among females and males of 20 or 40 years and older. Blue area: 95% confidence intervals. Exposure range limited to 333-20,000 #/cm³.

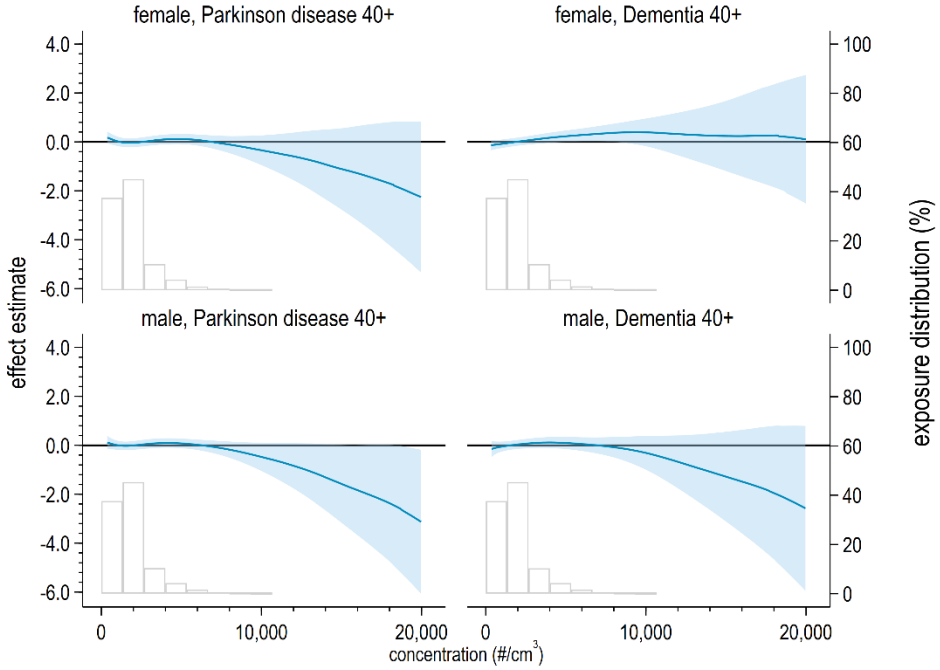


Figure A.5.3 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of neurodegenerative diseases among females and males of 40 years and older. Blue area: 95% confidence intervals. Exposure range limited to 333-20,000 #/cm³.

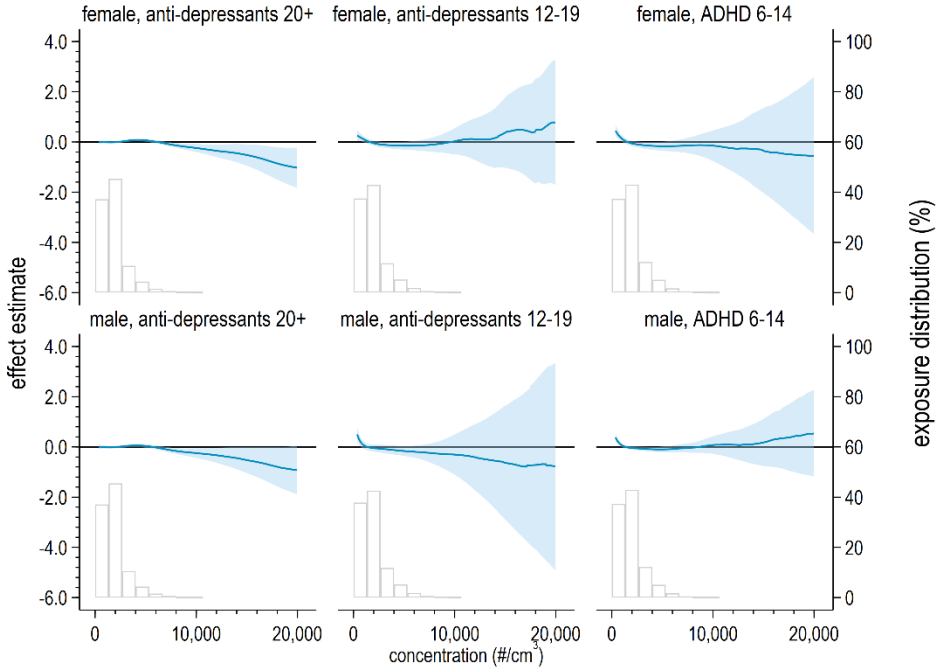


Figure A.5.4 Natural cubic splines (3 df) for associations between UFP from aviation and the incidence of anti-depressants among 20 years and older and 12-19 year olds and medication for ADHD of 6-14 year olds. Blue area: 95% confidence intervals. Exposure range limited to 333-20,000 #/cm³.

6 Public health monitor (PHM)

6.1 Objectives

The ***first objective*** of this study is to investigate the associations between long-term residential exposure to UFP from aviation and (self-reported) health in adult residents in the study area that participated in the 2012 and 2016 national health survey (Public Health Monitor 2012 and 2016, PHM (*'Gezondheidsmonitor Volwassenen GGD-en, CBS en RIVM'*).

The PHM includes information on lifestyle factors (e.g. smoking, alcohol use, BMI and physical activity), which is not available in the other registries. Therefore, the ***second objective*** of the study is to use the PHM to gain insight into potential residual confounding by incomplete adjustment for these factors in the studies on mortality and medication use (see paragraph 2.12).

6.2 Methods

6.2.1 Study design and study population

We used cross-sectional data from two national health surveys (Public Health Monitor 2012 and 2016, PHM (*'Gezondheidsmonitor Volwassenen GGD-en, CBS en RIVM'*) to study the association between long-term exposure to UFP from aviation and self-reported health. The PHM is a standardised questionnaire survey among adults (aged ≥ 19 years), with ~376,000 respondents in 2012 and ~450,000 in 2016. The survey is conducted every four years by all municipal health services (GGD) in the Netherlands in collaboration with RIVM and CBS. The PHM covers issues related to personal characteristics, lifestyle, socioeconomic status and physical and mental health. We selected all inhabitants who lived within the study area on September 1st[10] of 2012 or 2016, and who had complete information on residential history in the year of the survey as well as the 4 years before the survey (i.e. 2008-2012 and 2012-2016). We excluded subjects for whom the primary address in the year of the survey was outside the study area. In addition, we excluded subjects with missing data for more than one of the following variables: smoking status, alcohol use, level of physical activity and BMI (see paragraph 6.2.6.1). This resulted in a study population of 90,880 adults (36,617 in 2012 and 54,263 in 2016).

6.2.2 Health outcomes

In both years, the PHM addressed self-perceived general health (SGH). We used the following question to define SGH: "In general, would you say that your health is…" with possible responses being: very good / good / moderate / poor / very poor. To identify people with a poor SGH, we dichotomized answers, with a cut-off at less than moderate (very good + good + moderate versus poor + very poor).

[10] The surveys were carried out in de period September-December. A fixed survey date of September 1 is used for all data linkages.

Both PHM also include questions developed to screen for non-specific psychological distress based on the Kessler psychological distress scale (K10) (Kessler et al., 2002). The K10 is based on 10 questions about anxiety and depressive symptoms experienced during the past 30 days. Scores on the K10 range from 10 to 50. We dichotomized scores on the K10 to identify people with severe levels of psychological distress (score ≥ 30).

The Public Health Monitor 2012 also included questions on diabetes, asthma and COPD, hypertension, stroke, heart attack and other severe heart disorders. The questions are:

- "Do you have diabetes?"
- "Have you ever had a stroke, cerebral haemorrhage or cerebral infarction?"
- "Have you ever had a heart attack?"
- "Did you in the last 12 months have asthma or COPD (chronic bronchitis or lung emphysema?"
- "Did you in the last 12 months have hypertension?"
- "Did you in the last 12 months have another severe heart disorder (like heart failure or angina pectoris)?".

These questions (except on other severe heart disorders) are followed by a question "Have you been treated or monitored by a general practitioner or specialist for this in the past 12 months?". An exception is the question on another severe heart disorder, where the follow-up question does not re-specify the last 12 months. We used the question about treatment by a physician to define the health outcomes. The questions on diabetes, asthma and COPD, hypertension, stroke, heart attack and other severe heart disorders were not included in the core questionnaire of the Public Health Monitor 2016.

In addition, we analysed the prevalence of medication use. We linked medication use in the year of the survey, for the same medication groups as included in the study on the incidence of these medication groups (see chapter 5).

We included self-reported perceived health and psychological distress as primary endpoints, as these endpoints are not available in any of the other registries. The other self-reported health outcomes (only available for 2012) and medication use, we included as secondary endpoints and are mainly used to support results of similar outcomes in the other registries.

Table 6.1 Provides an overview of the primary and secondary outcomes.

Table 6.1 Overview of primary and secondary outcomes.

Outcome	PHM2012	PHM2016
Primary endpoints	**Self-reported**: Self-perceived poor general health (SPH) Severe psychological distress	**Self-reported:** Self-perceived poor general health (SPH) Severe psychological distress
Secondary endpoints	**Medication use[1] for (ATC):** - Asthma/COPD (R03A-RO3D) - Anti-depressants (NO6A) - Diabetes (A10A; A10B) - Heart disease (C01A-C01E; C03C) - Hypertension (C02A,C,D,K; C03A,B,D,E; C07A,B,C,F; C08C,D,G; C09A,B,C,D,X) **Self-reported, treated by a physician**: - Diabetes - Hypertension - Stroke - Heart Attack - Other heart disorder - Asthma / COPD	**Medication use for (ATC):** - Asthma/COPD (R03A-RO3D) - Anti-depressants (NO6A) - Diabetes (A10A; A10B) - Heart disease (C01A-C01E; C03C) - Hypertension (C02A,C,D,K; C03A,B,D,E; C07A,B,C,F; C08C,D,G; C09A,B,C,D,X)

1 From registry; see chapter 5.

The analyses for medication use for heart disease and self-reported stroke, heart attack and other heart disorders were restricted to the population ≥40 years of age, because of the low prevalence of these outcomes in the younger age groups.

6.2.3 *Assessment of exposure to UFP from aviation*

We describe in detail the modelling of exposure to UFP from aviation in Chapter 2.5. As indicated in paragraph 2.5.3, we calculated monthly average UFP contributions from aviation for all addresses in the modelling area, for the period from 2003 to 2019. This allows calculation of different exposure windows, including incorporating residential history.

For all subjects, we derived the address at the time of the questionnaire (set on September 1 of the year of the survey) as well as the primary address in each of the 4 preceding years, Next, we linked the corresponding annual average UFP contributions from aviation, and calculated 3- and 5-year multi-annual average. In addition, the annual average based on monthly values for the 12 months before the time of the questionnaire (September-August) was linked, to be used in sensitivity analyses in the analysis of self-reported health.

Additionally, to get an indication of peak exposures, we calculated the 1, 3 and 5 year annual average of hours per month with UFP concentrations higher than 66,667 #/cm^3 (see 2.5.4).

As estimates of UFP contributions from aviation are not available for addresses outside the modelling area, we set these values to 267 for the annual averages (i.e. 2/3 of the lowest value within the modelling area). We set hours with peak exposure to zero for these addresses.

6.2.4 Potential confounders
See also paragraph 2.6.

6.2.4.1 *Information available at personal or household level*
We included registry data, available at Statistics Netherlands, on age, gender, marital status, migration background, and household income. The survey included information on paid occupation (yes/no), smoking habits (current, former, never), number of cigarettes smoked per day (2012 only), alcohol use (current, former, never), number of glasses of alcohol per week, BMI and physical activity. In a cross-sectional study, lifestyle factors could be a cause or a result of poor health. Adjustment for these lifestyle factors could introduce a "cause-and-effect" bias. This is more likely to occur with mental health-related outcomes compared to the other outcomes. Literature suggests potential bidirectional relations of poor mental health with alcohol consumption (glasses) and the number of cigarettes smoked, but not with smoking status or alcohol use. We therefore included smoking status and alcohol use as confounders (model 2b onward) in the analysis of SPH, psychological distress and use of anti-depressants and added information on the number of glasses of alcohol per week in the analyses of the other outcomes. Number of cigarettes smoked per day was only available for the PHM 2012 and was therefore added in the sensitivity analysis for medication use and in the selection of the main model for the other self-reported outcomes (also only available for 2012).

6.2.4.2 *Information available at area level*
We selected the following indicators:

- Mean income per inhabitant.
- Number of people with unemployment benefit (per 1000 inhabitants aged 15-64 years).
- Number of inhabitants with social assistance (per 1000 households).
- Percentage of inhabitants with a non-western migration background.
- Education (3 categories expressed in percentage: high, mid, low).
- Degree of urbanisation (5 categories).

We linked all indicators to the primary address in the year of the survey. We used information for the year of the survey for all indicators, with the exception of education for which we linked information for 2013 to the PHM 2013. We linked all indicators at neighbourhood (*buurt*) level, which is the smallest available area, and categorized those into quintiles.

6.2.5 Other air pollutants and transportation noise

6.2.5.1 *Air pollution*

We included the annual average concentrations of PM2.5, NO_2, and EC as co-pollutants in our study. More information on co-pollutants modelling methodology is provided in Chapter 2.7.

6.2.5.2 *Transport noise*

We included annual average aviation noise levels from Schiphol, as well as road traffic and railway noise exposures. More information on noise exposure assessment is available in Chapter 2.7.

6.2.6 Statistical analyses

6.2.6.1 Missing data

We performed multiple imputations of missing values using chained equations (MICE) to generate 20 datasets using 20 iterations. All variables used in the regression models were available in the imputation procedure, plus some auxiliary variables (degree of urbanization, medication use for the different defined endpoints). Due to the non-randomness of missing values for lifestyle-related variables in the data, we excluded subjects who had more than one missing value for the variables smoking status, alcohol use, physical activity and BMI from the study (817 subjects for PHM 2012 and 1,712 subjects for PHM 2016).

6.2.6.2 Main analyses

As described in paragraph 2.8.2 we defined several models with increasing covariate adjustment. Model 1 included: age and sex. Model 2 further included individual covariates: marital status, migration background, household income, education and paid occupation. In model 2b, we added information on smoking, alcohol use, BMI and physical activity (see 6.2.4.1). Model 3 further expanded model 2b with indicators for neighbourhood-level SES. As some of these indicators were highly correlated (see tables 6.5a&b) we performed an exploratory analysis for the primary outcomes in which we added step-by-step area-level SES covariates until the mode fit (described by AIC) did not improve anymore, paying attention to the direction of the area-level covariate associations. Based on the results of these exploratory analyses, we included the variables mean income and percentage of inhabitants with a non-western migration background in model 3. Model 4 additionally adjusted for GGD region.

The selection of the main model was based on the results of model 4. We selected the most appropriate exposure window by comparing model fit (AIC) for 1 year and 3- and 5-year moving averages of UFP from aviation. Based on this examination, we chose model 4 with 1-year average exposure in the year of the survey as the main confounder model.

We evaluated the shape of the exposure-response curves by using natural splines with 3 degrees of freedom.

6.2.6.3 Multi-exposure models

Other air pollutants

We used annual average concentrations of PM2.5, NO_2, and EC in the year of the survey, i.e. the same exposure window as used for UFP from aviation. As EC is included in PM2.5, we also considered the difference between PM2.5 and EC (*i.e.*, PM2.5-EC) as a potential exposure variable. Due to correlations between the air pollutants (Table 6.5), we included PM2.5, NO_2, and EC separately in two-pollutant models.

Transport noise

Exposure to transport noise (aviation, road, and rail traffic) may contribute to the risk of some of the health endpoints that are studied for UFP and was therefore included as a potential confounder in multi-pollutant models. In four-pollutant models, we adjusted UFP from aviation for all available noise variables.

As described in detail in paragraph 2.10, we included noise level thresholds at which the health risks may start, to account for the possibility that at lower levels, transport noise may no longer be distinguishable from the background noise and the potential risk of this source might be assimilated. We used 53 dB L_{den} as a threshold and assigned a value of 53 dB L_{den} to all noise levels < 53 dB L_{den}. For L_{night} we used a threshold of 43 dB.

6.2.6.4 (Other) sensitivity analyses and stratifications

We performed a number of sensitivity analyses to investigate the robustness of the results. We performed the following analyses:

- Evaluate peak exposure to UFP from aviation by using the number of hours above 66,667 #/cm^3 (instead of an annual average concentration; see 2.5.4). These results are included in the section on results for the different exposure windows.
- Exclusion of subjects who lived in the municipality of Amsterdam in the year of the survey.
- Exclusion of subjects who lived in one of three municipalities (Velsen, Beverwijk and Heemskerk) around a major industrial source in the IJmond region.
- Exclusion of subjects who lived in the 4 municipalities with the lowest average UFP exposure.
- Exclusion of subjects who moved in the 5 years before the survey.
- Limiting the statistical analysis to participants with a Dutch background.
- Exclusion of subjects with imputed data (complete case analyses).
- Adjusting for urbanization (5 categories).
- Stratification for urbanization; high (categories 1-2) vs. low (categories 3-5) urbanization.
- Stratification by age at the time of the survey (< 65 vs. ≥ 65 years).
- Stratification by sex.
- Stratification by year of the survey (2012 vs. 2016).

6.2.6.5 Additional analyses to evaluate potential residual confounding due to incomplete adjustment for lifestyle factors

The PHM includes information on lifestyle factors (e.g. smoking, alcohol use, BMI and physical activity), which is not available in the other registries. Therefore, we used the PHM to gain insight into potential residual confounding by incomplete adjustment for these factors in the studies on mortality and medication use.

We evaluated the effect of adjustment for smoking, alcohol use, BMI and physical activity on the associations between UFP from aviation in the analyses of the PHM. This includes the (self-reported) health endpoints within the PHM as well as the *prevalence* of medication use for medication groups included in the study on the *incidence* of these medication groups. For this, we used a model that only includes covariates that are also available in the studies on mortality and medication use, i.e. age, sex, marital status, migration background, household income and indicators for neighbourhood SES. We compare effect estimates for this model with effects estimates of the fully adjusted models (including education, paid occupation and lifestyle factors).

In addition, we evaluated the effect of adjustment for smoking, alcohol use, BMI and physical activity on associations between UFP from aviation and natural cause mortality in the *PHM 2012*. We did not conduct this analysis in the PHM 2016 as only 3 years of follow-up for mortality is available (2,478 deaths; 4,9%). In addition, no information is available on the number of cigarettes smoked by current smokers in the PHM 2016.

Furthermore, we indirectly adjusted for smoking status and BMI of associations with mortality, using the indirect adjustment technique as developed by Shin et al (2014), and applied in ELAPSE (Stafoggia et al, 2022). The method uses information contained within the health monitor regarding the multivariate relationships between the missing lifestyle covariates (dependent variable) and UFP from aviation, adjusting for observed covariates in the main model of the mortality study. We drew a randomly stratified sample of the PHM 2012 and 2016 with distribution of covariates (age, sex, marital status, migration background, household income) similar to the study population in the mortality study. The combined sample included 3,333 observations. We obtained effect estimates for associations of smoking status and BMI with non-accidental mortality from a European cohort of more than 300,000 adults in the ELAPSE study (Brunekreef et al, 2021).

For further interpretation of potential bias, we specified linear models in the survey sample with the exposure as the dependent variable and lifestyle covariates (e.g. smoking status, BMI) and all covariates included in the main model as independent variables. This provides insight into potential differences in UFP exposure for, among others, current smokers compared to never smokers and obese people compared to normal weight people. We conducted these analyses within the stratified sample used for the indirect adjustment for mortality (n=3,333). In addition, we created two subsets that could provide insight in potential bias in the study on pregnancy outcomes:

1. all women that were pregnant at the date of the survey (irrespective of the duration of the pregnancy at that time) (n=550) and
2. a stratified sample of all women that participated in the health monitor, with the same distribution in age, education and migration background as the mothers in the study on pregnancy outcomes (n=3,064).

The first subset did not include sufficient subjects to allow further stratified sampling on covariates. The second subset included mainly non-pregnant women and was used to confirm findings in the first subset in a larger population.

6.3 Results

6.3.1 Study population

The study population consisted of 90,880 subjects (36,617 subjects in 2012 and 54,263 subjects in 2016). Characteristics are presented in table 6.2a and 6.2b.

The PHM 2016 included more subjects aged>65 (52%) and fewer subjects with paid occupations (42%) compared to the PHM 2012 (39% and 51% respectively). Other characteristics were more similar.

In total, 18% of the subjects were current smokers (20% in 2012 and 17% in 2016). In 2012, the average number of cigarettes smoked per day was 11. The follow-up question on the number of cigarettes smoked by current smokers was not included in the core questionnaire of the Public Health Monitor 2016.

About 14% of the subjects had missing values in any of the individual covariates that were used in the analyses of the primary outcomes (see 6.2.4.1). Of the subjects with complete cases for those covariates, an additional 2% (849 subjects in 2012 and 2094 in 2016) had missing values on the number of glasses of alcohol per week. Additionally, in the PHM 2012, 939 (3%) subjects had missing values for the number of cigarettes smoked per day (PHM2012 only). Missing values were imputed using multiple imputations by chained equations (MICE).

We did not observe any substantial differences in the distribution of the individual covariates between the full imputed dataset and the complete cases (see appendix; tables A6.1a&b).

Table 6.2a Characteristics of the study population in the imputed dataset: Individual covariates.

	2012 (n=36,617) %	**2016** (n=54,263) %	**Total** (n=90,880) %
Sex: Male	44.5	44.7	44.6
Age[2]			
19-39	21.1	16.4	18.3
40-64	39.9	31.7	35.0
≥65	39.1	51.9	46.7
Marital status			
Married/living together	57.2	56.5	56.8
Unmarried/never married	23.8	21.4	22.4
Divorced	9.8	11.2	10.6
Widowed	9.2	10.9	10.2
Migration background			
Dutch	82.3	82.2	82.3
Netherlands Antilles	0.4	0.5	0.4
Suriname	2.1	1.9	2.0
Turkey	1.6	1.1	1.3
Morocco	1.3	0.8	1.0
Other, western	9.6	10.5	10.1
Other, non-western	2.7	3.1	3.0
Education			
Low	40.6	38.1	39.1
Medium	28.9	29.5	29.2
High	30.5	32.4	31.7
Household income[2]			
≤ 1 percentile	0.3	0.3	0.3
2-5 percentile	1.4	1.2	1.3
5-10 percentile	2.2	2.3	2.3
10-25 percentile	10.5	11.6	11.2
25-50 percentile	23.4	25.4	24.6
50-75 percentile	28.1	26.3	27.0
75-90 percentile	19.3	18.3	18.7
90-95 percentile	7.3	7.1	7.2
95-99 percentile	6.1	6.0	6.1
>99 percentile	1.4	1.4	1.4

[2] Included in the analyses in 12 categories.

Table 6.2b Characteristics of the study population in the imputed dataset: Individual covariates, not available in any of the other sub-studies.

	2012 (n=36,617) %	**2016** (n=54,263) %	**Total** (n=90,880) %
Smoking status			
Current	19.9	16.7	18.0
Former	37.5	41.3	39.8
Never	42.6	42.0	42.2
# cigarettes smoked for current smokers (mean (sd))	11.2 (8.1)	N.A.	
Alcohol use			
Current	83.3	83.3	83.3
Former	5.5	6.2	5.9
Never	11.2	10.6	10.8
# of alcohol glasses/week for current consumers (mean (SD))	8.9 (9.7)	8.7 (9.7)	8.8 (9.7)
BMI			
< 18.5 kg/m^2	1.3	1.5	1.4
18.5-24.9 kg/m^2	47.4	46.6	46.9
25.0-30.0 kg/m^2	38.1	37.9	38.0
>30 kg/m^2	13.2	14.0	13.7
Physical activity			
≤180 min/week	28.2	23.5	25.4
180 – 480 min/week	27.4	24.7	25.8
480 – 1050 min/week	22.3	25.3	24.1
>1050 min/week	22.1	26.5	24.8
Paid occupation			
Yes	50.5	41.7	44.9
No	49.5	58.3	55.1

[1] In the imputed dataset.

6.3.2 *Health outcomes*

Table 6.3.a presents the prevalence of the different self-reported health outcomes; table 6.3b includes the prevalence of medication use for medication groups included in the substudy on incidence.

Consistency between self-reported, physician treated, disease in the PHM 2012 and medication use was high for diabetes, as also observed for the full PHM 2012 by Strak et al (2017b). Two-by-two tables are presented in the appendix; table A6.2. Of the subjects with self-reported diabetes, 87% also had prescribed diabetes medication; of the subjects with prescribed diabetes medication, 94% had also positively answered the survey question about having a physician diagnosis of diabetes. For self-reported asthma and hypertension, the percentages also having medication were similar (84% and 92%, respectively), but the percentage of subjects with prescribed medication with a positive

answer to the survey question was substantially lower: 54% for asthma/COPD and 63% for hypertension.

For the PHM 2012, 3,890 (10.4%) subjects had died by 31-12-2019 (2,478 (8.3%) of the complete cases); For the PHM 2016, this was the case for 2,741 (4.9%) of the subjects (1,832 (4.0%) of the complete cases).

Table 6.3a Prevalence of self-reported health outcomes in the study population (primary outcomes in bold).

Primary outcomes	**2012** (n=36,617) %	**2016** (n=54,263) %	**Total** (n=90,880) %
Self-perceived poor general health (SPH)	**1,416 (3,9)**	**2,607 (4,8)**	**4,023 (4.5)**
Severe psychological distress	**1,631 (4,6)**	**2,769 (5,1)**	**4,400 (4.9)**
Secondary outcomes			
Diabetes	2,841 (8.0%)	NA	
Hypertension	7,082 (21.0%)	NA	
Stroke	263 (0.7%)	NA	
Heart attack	1,053 (3.0%)	NA	
Other severe heart disorder	1,223 (3.4%)	NA	
Asthma or COPD	2,232 (6.6%)	NA	
Population ≥40	N=28,906		
Stroke	259 (0.9%)		
Heart attack	1,040 (3.7%)		
Other severe heart disorder	1,199 (4.3%)		

[1] In the imputed dataset.

Table 6.3b Prevalence of medication use for medication groups1

	2012 (n=36,617) %	**2016** (n=54,263) %	**Total** (n=90,880) %
Diabetes	2,774 (7.6%)	4,679 (8.6%)	7,453 (8.2%)
Hypertension	11,587 (31.6%)	19,449 (35.8%)	31,036 (34.2%)
Heart disease	2,744 (7.5%)	4,573 (8.4%)	7,317 (8.1%)
Anti-depressants	2,454 (6.7%)	3,802 (7.0%)	6,256 (6.9%)
Asthma / COPD	3,828 (10.5%)	5,865 (10.8%)	9,693 (10.7%)
Population ≥40	N=28,906	N=45,390	N=74,296
Heart disease	2,710 (9.4%)	4,539 (10.0%)	7,249 (9.8%)

[1] See table 6.1 for ATC codes.

6.3.3 Exposure

6.3.3.1 Distribution of UFP from aviation, other air pollutants and noise

Table 6.4 presents the distribution of UFP from aviation, other air pollutants and noise for the combined dataset (n=90,880); distributions for the 2012 and 2016 separately are included in the appendix (Tables A6.3a&b).

Residential exposure to UFP from aviation was higher for the PHM 2016 (mean 2,204 #/cm^3) compared to the PHM 2012 (mean 1,745 #/cm^3). This is related to higher levels of UFP in the study area as a whole in 2016 compared to 2012 (due to differences in meteorological circumstances and flight movements). Average levels of the other air pollutants were lower in 2016 compared to 2012, while aviation noise from Schiphol (both Lden and Lnight) was higher in 2016.

For aviation noise from Schiphol and rail traffic, about 5% of the population was exposed to levels above 53 dB (Lden) and 43 dB (Lnight). For road traffic, this percentage was substantially higher (>40%).

6.3.3.2 Correlation between UFP from aviation, other air pollutants, noise and neighbourhood SES

Table 6.5 presents Spearman correlation coefficients between UFP from aviation, other air pollutants, noise and indicators for neighbourhood SES.

UFP from aviation was poorly correlated with most of the other exposure and indicators for area-level SES. The highest correlation was observed with aviation noise from Schiphol (L_{den}; R=0.31).

Average residential concentrations of the co-pollutants (PM2.5, NO_2 and EC) were highly correlated.

Between the different indicators for area-level SES, we observed high negative correlations between %high and %low education (R= -0.81), and between mean income and low education (R= -0.71) or social assistance (R= -0.75). We observed a high positive association between mean income and %high education (R= 0.70) and between %non-western and social assistance (R= 0.76).

24-hour average noise levels (L_{den}) and 8-hour night-time noise levels (L_{night}) were highly correlated: R=0.82; 0.94 and 0.99 for aviation noise from Schiphol, rail traffic and road traffic respectively. Correlations between L_{night} and air pollution or indicators for neighbourhood SES were very similar to those observed for L_{den}. We observed the largest difference in the correlation with UFP and aviation noise from Schiphol, which was lower for L_{night} compared to L_{den} (0.11 and 0.31 respectively).

6.3.3.3 Distribution of UFP from aviation per degree of urbanisation

Table 6.6 presents the distribution of UFP from aviation for the different categories of degree of urbanisation. About 65% of the population lived in a highly urbanized neighbourhood (>1,500 addresses/km^2). We observed no clear pattern of increasing or decreasing UFP concentrations with degree of urbanisation.

6.3.3.4 Correlation between different exposure metrics for UFP from aviation

Table 6.6 presents Spearman correlation coefficients between the different exposure metrics for UFP from aviation. All exposure metrics were highly correlated (R≥0.8).

Table 6.4 Distribution of UFP from aviation, other air pollutants and noise (n=90,880) (UFP in #/cm^3; other air pollutants in µg/m^3, noise in dB).

	Mean	SD	p1	p5	p10	p25	p50	p75	p90	p95	p99
UFP	**2,019**	**1,339**	**681**	**844**	**977**	**1,241**	**1,634**	**2,202**	**3,545**	**4,646**	**7,739**
Other air pollutants											
PM25	12.3	1.6	10.0	10.4	10.6	11.0	11.7	13.8	14.4	14.8	16.3
NO_2	23.1	3.8	15.5	17.4	18.5	20.3	22.8	25.4	28.1	30.0	32.9
EC	0.9	0.2	0.6	0.7	0.7	0.8	0.9	1.0	1.1	1.2	1.4
PM2.5-EC	11.4	1.5	9.3	9.7	9.8	10.1	10.7	12.9	13.3	13.7	14.9
Noise											
Lden Schiphol	46.9	3.7	40.8	41.7	42.6	44.4	46.3	48.7	52.1	53.9	57.8
Lden Road	52.8	6.3	40.5	43.7	45.3	48.2	52.0	56.7	61.6	64.3	68.9
Lden Rail	34.9	9.0	24.0	24.0	24.0	26.9	33.9	40.4	47.4	51.6	59.1
Lnight Schiph	35.3	4.0	28.1	29.2	30.6	32.7	34.6	37.3	41.3	43.5	46.6
Lnight Road	43.2	6.4	31.3	34.3	35.9	38.6	42.3	47.2	52.4	55.3	60.1
Lnight Rail	26.5	8.6	19.0	19.0	19.0	19.0	23.8	32.2	39.0	43.3	50.8

Table 6.5 Spearman correlation between UFP aviation, other air pollutants, noise and indicators for neighbourhood SES.

	Other air pollutants					**Noise (Lden)**				**Neighbourhood SES**					
	PM2.5	NO_2	EC	PM2.5- EC		Aviation (Schiphol)	Road traffic	Rail traffic		High edu.	Low edu.	Income	Unemployment	Social assistance	%non-western
UFP-aviation	-0.18	-0.02	-0.03	-0.20		0.31	0.07	-0.15		0.04	-0.01	0.12	0.04	-0.07	0.01
PM2.5	1.00	0.81	0.69	1.00		-0.14	0.14	0.16		0.08	0.00	-0.10	0.05	0.25	0.33
NO_2		1.00	0.93	0.78		-0.11	0.31	0.26		0.23	-0.11	-0.04	0.06	0.27	0.45
EC			1.00	0.64		-0.14	0.34	0.32		0.30	-0.15	-0.05	0.12	0.31	0.52
PM2.5-EC				1.00		-0.14	0.11	0.14		0.05	0.02	-0.11	0.05	0.24	0.32
Aviation noise						1.00	-0.03	-0.21		-0.17	0.09	0.03	-0.09	-0.12	-0.09
Road traffic noise							1.00	0.13		0.11	-0.08	0.03	0.02	0.05	0.07
Rail traffic noise								1.00		0.24	-0.22	0.04	0.09	0.08	0.12
%High Education										1.00	-0.81	-0.71	-0.26	-0.35	-0.14
%Low education											1.00	-0.75	0.30	0.50	0.31
Mean income												1.00	-0.40	-0.70	-0.54
Unemployment rate													1.00	0.51	0.41
Social assistance														1.00	0.76
%non-western															1.00

Table 6.6 Distribution of UFP from aviation stratified by degree of urbanization (in #/cm³).

PHM 2012	**n**	**Mean**	**Sd**	**p1**	**p5**	**p10**	**p25**	**p50**	**p75**	**p90**	**p95**	**p99**
1 (>2,500 addresses/km²)	28,939	1,933	1,067	650	805	870	1,214	1,738	2,246	3,269	4,145	6,057
2 (1,500-2,500 addresses/km²)	29,989	2,022	1,453	650	799	942	1,228	1,635	2,116	3,462	5,259	7,955
3 (1,000-1,500 addresses/km²)	15,271	2,108	1,509	793	1,015	1,124	1,377	1,577	2,101	3,955	4,941	9,037
4 (500-1,000 addresses/km²)	9,953	2,225	1,469	851	1,010	1,095	1,250	1,591	2,571	4,387	5,291	7,549
5 (<500 addresses/km²)	6,728	1,868	1,197	729	983	1,045	1,183	1,480	2,223	3,382	3,837	6,281

Table 6.7 Spearman correlation between different UFP exposure metrics (n=90,880).

UFP-aviation	**Average PNC (#/cm³)**			**Peak exposure[3]**
	Year of survey	**3 year average**	**5 year average**	**Year of survey**
Average year of survey	1.00	0.97	0.95	0.84
3 year average[1]		1.00	0.99	0.84
5 year average[2]			1.00	0.80
Peak exposure[3] in year of survey				1.00

[1] Exposure in the year of the survey and the 2 years prior to the survey, based on the primary address in each of the 3 years.
[2] Exposure in the year of the survey and the 4 years prior to the survey, based on the primary address in each of the 5 years.
3 #hours above 66,667 #/cm³ (see 2.5.4).

6.3.4 Associations between UFP from aviation and the primary outcomes

6.3.4.1 Main model

Figure 6.1 shows the results from the different confounders models for the association between UFP from aviation and the two primary endpoints. For both SPH and psychological distress, we observed a significant negative association in M1, which attenuated and lost statistical significance after further adjustment. Associations were similar for the other exposure specifications (figure 6.2). Pooled effect estimates for the two individual PHM were very similar to the effect estimates from the combined dataset (appendix table A6.4).

Concentration response functions for UFP and the two primary outcomes (figure 6.3) do not show strong deviations from linearity; for distress we observed a decreasing trend at the lowest concentrations, which crosses unity at about 1,300 #/cm^3. This pattern is no longer present when the 4 municipalities with the lowest UFP exposure are excluded (see appendix; figure A6.1a).

Associations were also similar after adjustment for other pollutants and noise (figure 6.4). Adjustment for co-pollutants using a spline with 3 degrees of freedom (instead of a linear function) had no noteworthy impact on either the effect estimates or the concentration-response functions (results not shown).

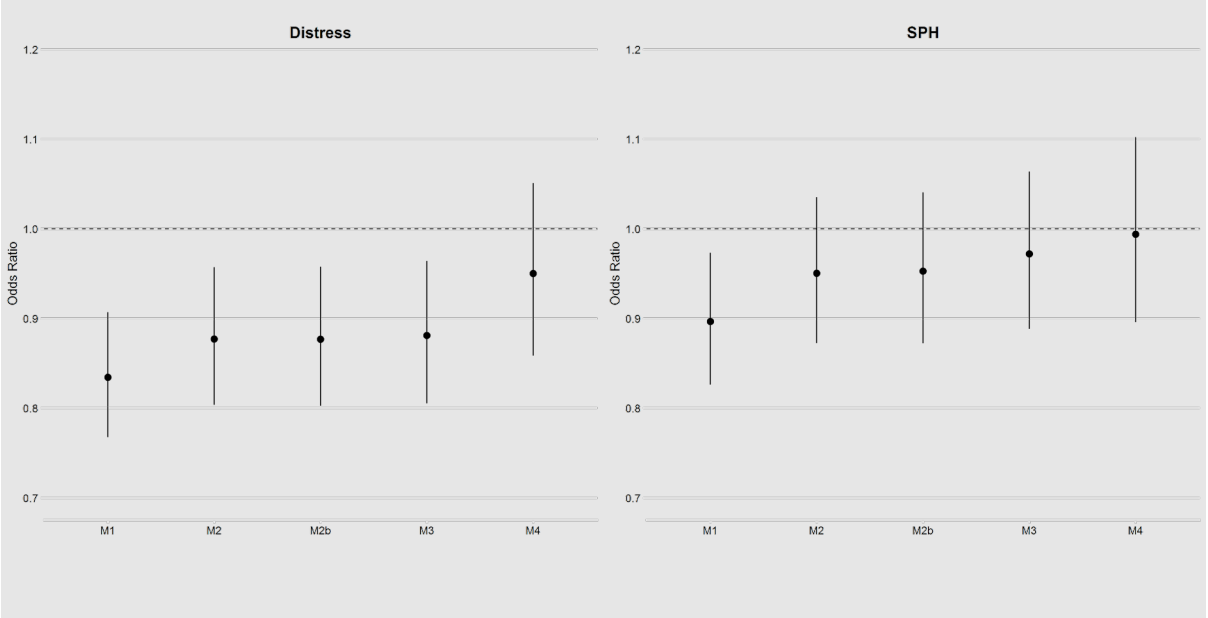


Figure 6.1 Associations between UFP from aviation and primary outcomes in different confounder models. (M1: adjusted for age, sex and year of the survey; M2: M1+ marital status, migration background, household income, education and paid occupation; M2b: M2 + smoking status, alcohol use, BMI and physical activity; M3: M2b + neighbourhood level mean income and percentage non-western; M4: M3 + GGD-region). Effect estimates expressed per 3,500 #/cm^3.

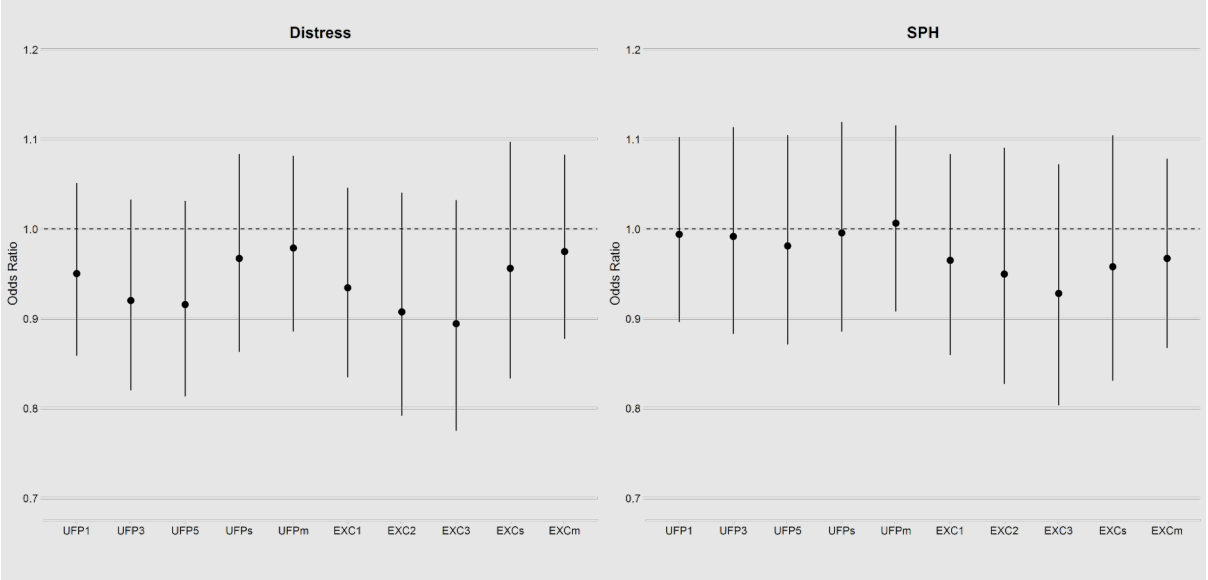


Figure 6.2 Associations between UFP from aviation and primary outcomes with different exposure specifications (UFP1: 1-year average exposure in the year of the survey; UFP3: 3 year average exposure; UFP5: 5 year average exposure; UFPs: 1 year average based on the 12 months before the time of the survey (September-August); UFPm: monthly average of the month before the time of the survey; EXC1: hours with peak exposure in the year of the survey. Other EXC same as for UFP). All models adjusted for age, sex, year of the survey, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, BMI, physical activity, neighbourhood level mean income, percentage non-western and GGD-region. Effect estimates expressed per 3,000 #/cm^3 for UFP and per 100 hours per month for EXC.

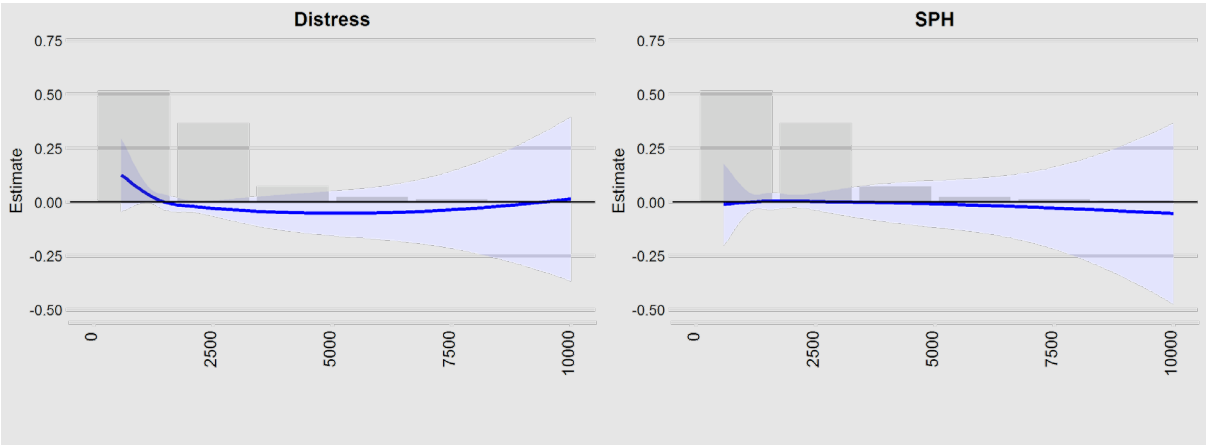


Figure 6.3 Natural cubic splines (3 df) for the association between UFP from aviation and primary outcomes. Shaded: 95% confidence interval. Histogram of exposure added to illustrate sparse data regions.

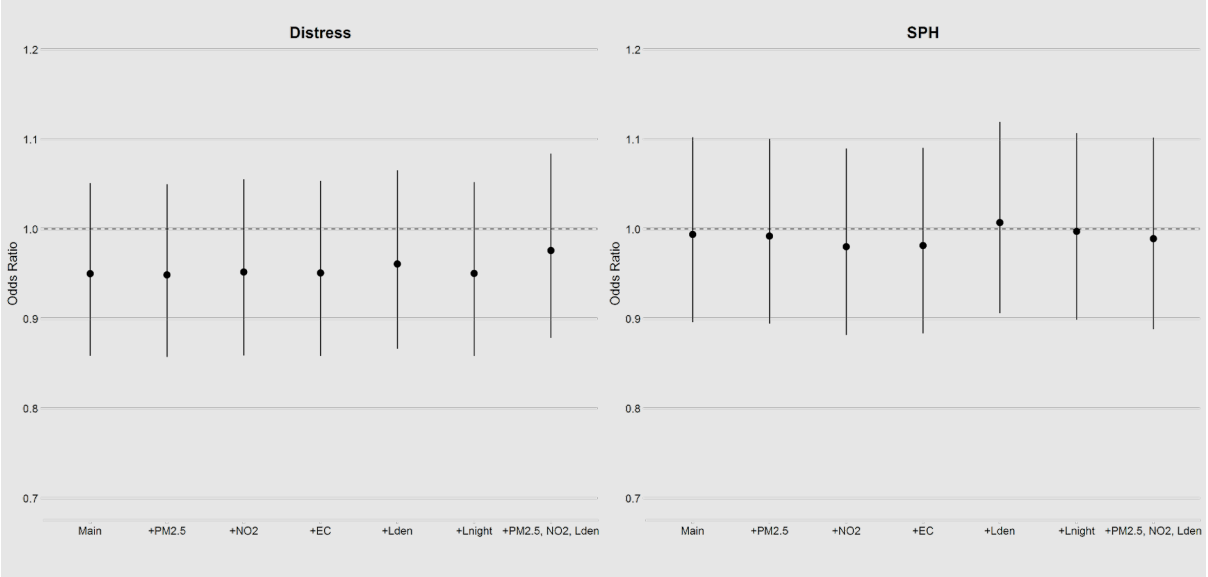


Figure 6.4 Associations between UFP from aviation after adjustment for co-pollutants and noise (Main: Main model (M4); +PM2.5: adjusted for PM2.5; +NO2: Adjusted for NO_2; +EC: adjusted for EC; +Lden: adjusted for 24-h average aviation noise from Schiphol, road traffic and rail traffic; +Lnight: adjusted for 8-h night-time noise from Schiphol, road traffic and rail traffic. All models adjusted for age, sex, year of the survey, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, BMI, physical activity, neighbourhood level mean income, percentage non-western and GGD-region. Effect estimates expressed per 3,500 #/cm^3.

6.3.4.2 Sensitivity analyses and stratifications

Results were generally robust in the different sensitivity analyses (figure 6.5); with exception of a statistically significant negative association that is observed when the population is limited to subjects with a Dutch background. Overall, results from the stratified analyses did not show much evidence for effect modification (figure 6.6).

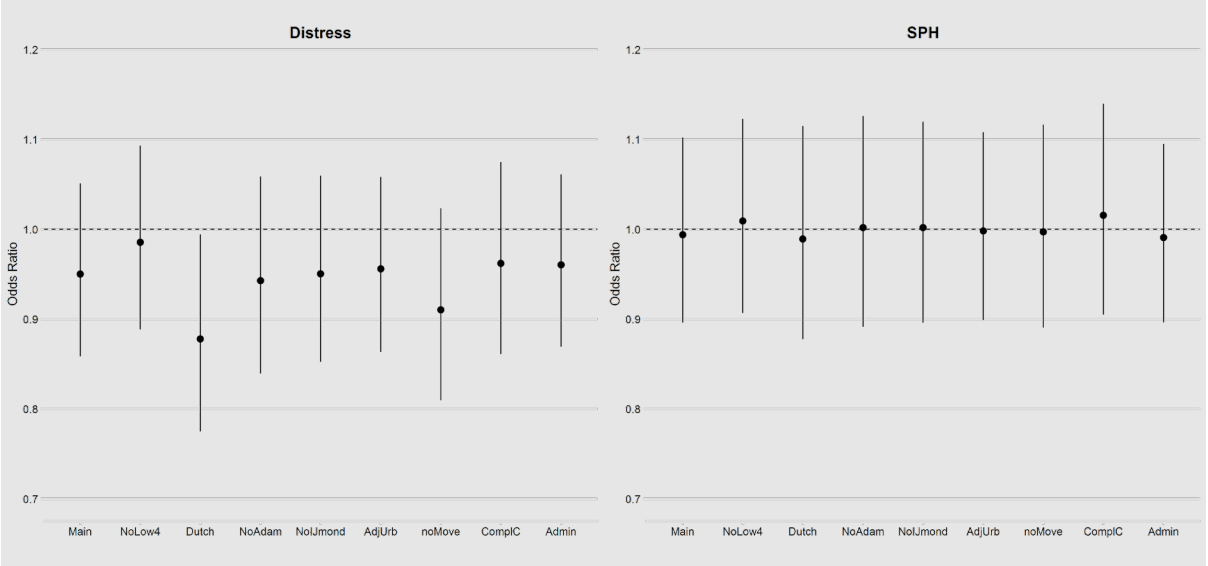


Figure 6.5 Associations between UFP from aviation and primary outcomes in sensitivity analyses. Main, NoLow4, NoAdam, NoIJmond, noMove and ComplC adjusted for age, sex, year of the survey, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, BMI, physical activity, neighbourhood level mean income and percentage non-western and GGD-region; Dutch: same as main, except migration background (only 1 level); AdjUrb additionally adjusted for degree of urbanization (5 categories); Admin: Model adjusted for covariates available in administrative record, i.e. age, sex, marital status, migration background, household income, neighbourhood level mean income and percentage non-western and GGD-region; Effect estimates expressed per 3,500 #/cm^3.

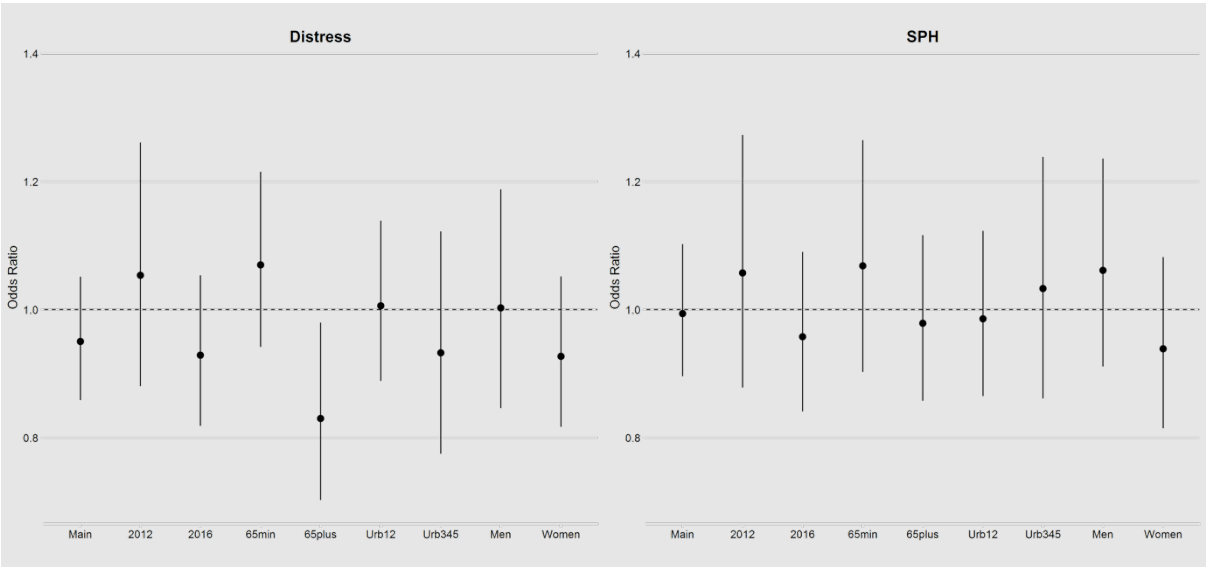


Figure 6.6 Associations between UFP from aviation and primary outcomes in stratified analyses. All models adjusted for age, sex, year of the survey, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, BMI, physical activity, neighbourhood level mean income and percentage non-western and GGD-region; Effect estimates expressed per 3,500 #/cm^3.

6.3.5 Associations between UFP from aviation and medication use

6.3.5.1 Main model

Figure 6.7 shows the results from the different confounders models for the association between UFP from aviation and the prevalence of prescribed medication in the year of the survey.

For medication for diabetes, effect estimates slightly increased with increasing covariate adjustment and effects estimates were statistically significant ($p<0.05$) in all models except M1.

Prescribed medication for hypertension was not statistically associated with UFP from aviation in models 1 to 3, but the effect estimate increased and became borderline ($p=0,051$) significant after further adjustment for GGD-region (M4).

Prescribed anti-depressants were significantly inversely associated with UFP from aviation in M1 and M3. However, this association attenuated and became non-significant after adjustment for GGD-region.

Medication for asthma and heart disease were not associated with UFP from aviation in any of the models.

Pooled effect estimates for the two individual PHM were very similar to the effect estimates from the combined dataset (appendix table A6.4).

Associations were similar for the other exposure specifications (figure 6.8). The association with medication for hypertension became statistically significant at the $p<0.05$ level when any of the other exposure metrics was used.

Figure 6.9 shows the concentration-response functions for UFP and medication use. Similar to the association for psychological distress, we observed a decreasing trend at the lowest concentrations for most outcomes, with the strongest deviation from linearity observed for diabetes and heart disease. For all outcomes except heart disease, this pattern is no longer present when the 4 municipalities with the lowest UFP exposure are excluded (see appendix; figure A6.1a).

Associations were also similar after adjustment for other pollutants and noise (figure 6.10). Adjustment for co-pollutants using a spline with 3 degrees of freedom (instead of a linear function) had no noteworthy impact on either the effect estimates or the concentration-response functions (results not shown).

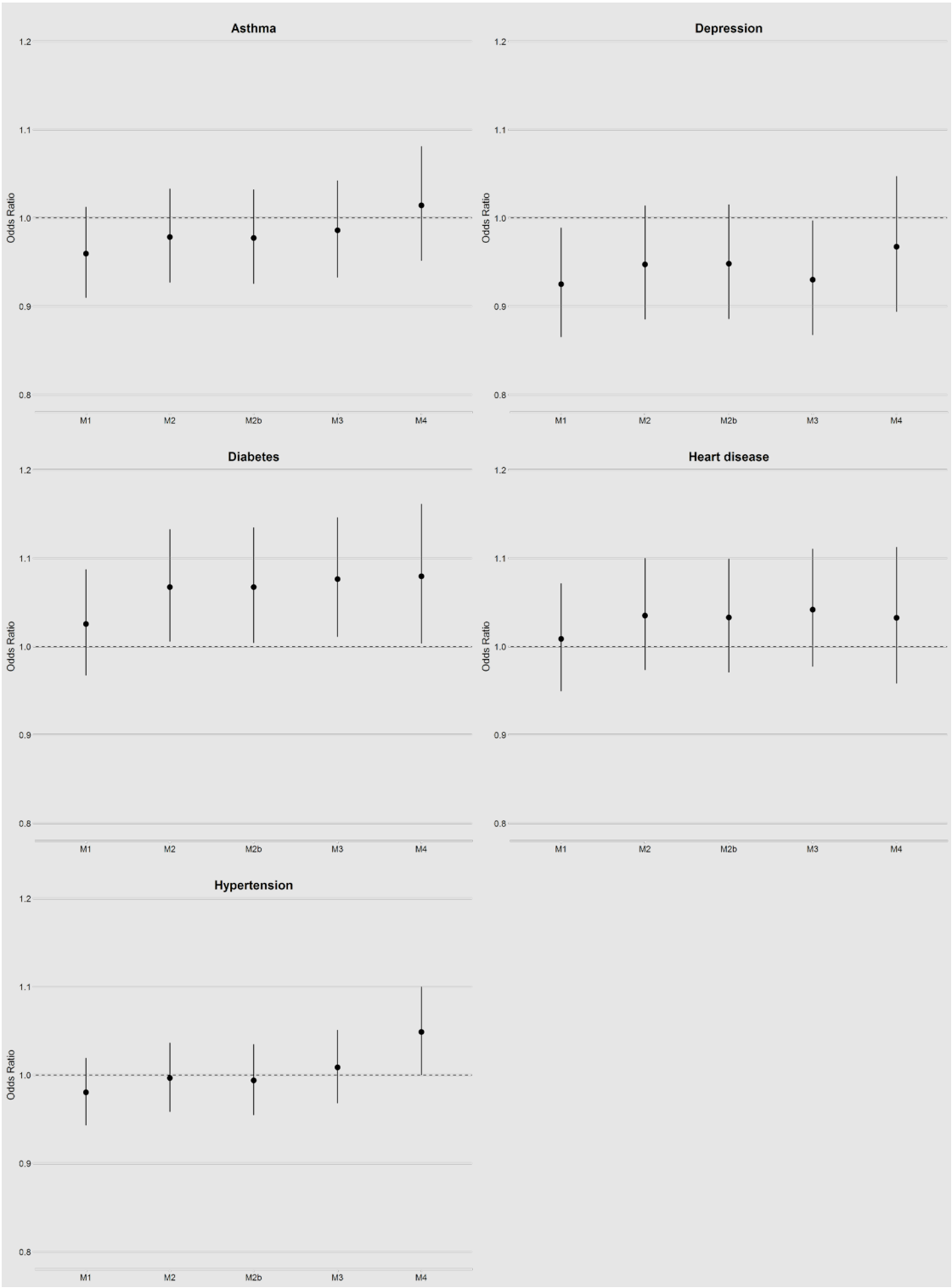


Figure 6.7 Associations between UFP from aviation and medication use in different confounder models. (M1: adjusted for age, sex and year of the survey; M2: M1+ marital status, migration background, household income, education and paid occupation; M2b: M2 + smoking status, alcohol use, #glasses of alcohol per week (except for depression, see 6.2.4.1), BMI and physical activity; M3: M2b + neighbourhood level mean income and percentage non-western; M4: M3 + GGD-region). Effect estimates expressed per 3,500 #/cm^3.

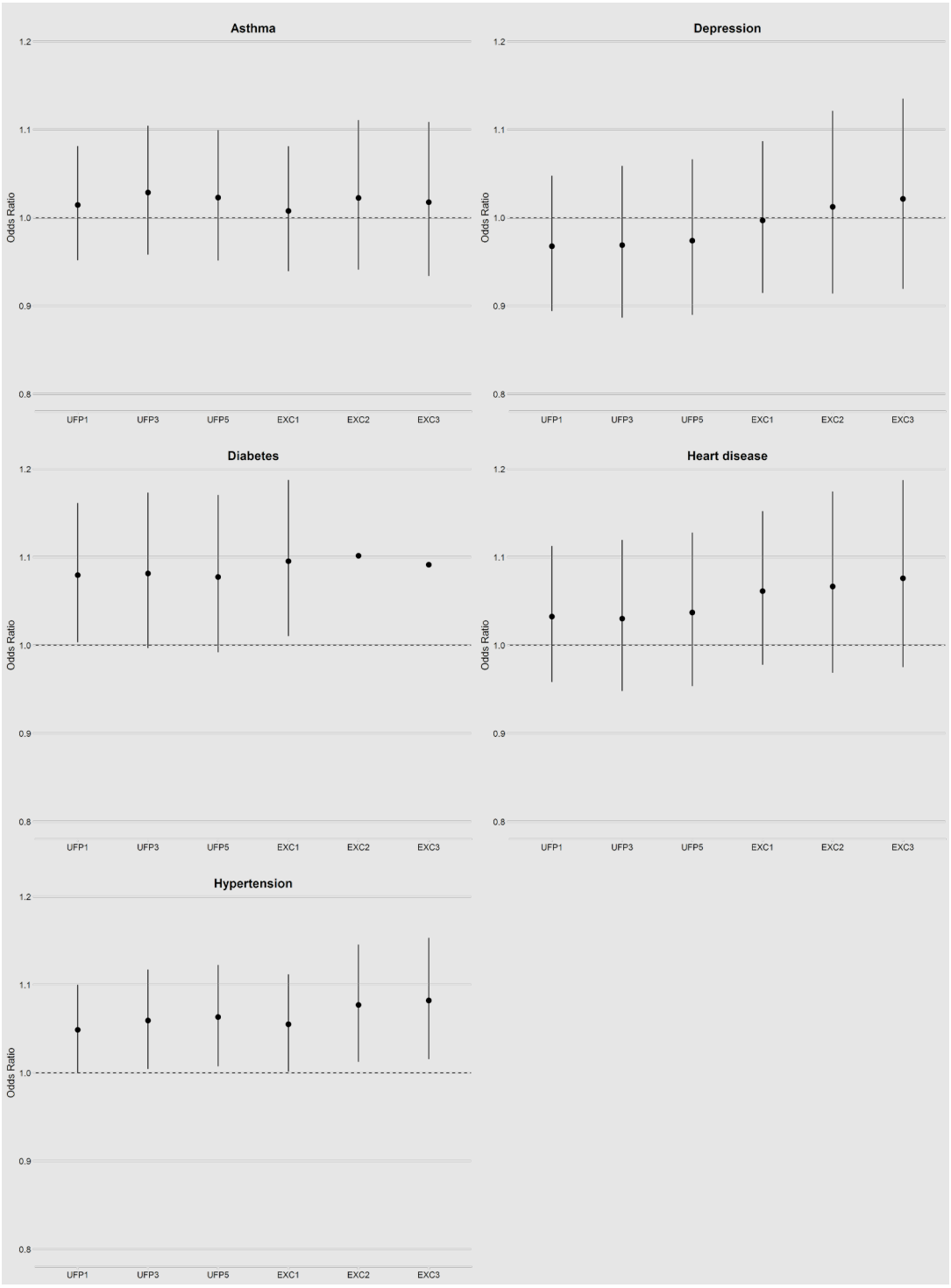


Figure 6.8 Associations between UFP from aviation and medication use for different exposure variables. (UFP1: 1-year average exposure in the year of the survey; UFP3: 3 year average exposure; UFP5: 5 year average exposure; EXC1: hours with peak exposure in the year of the survey; EXC3: 3 year average; EXC5: 5 year average). All models adjusted for age, sex, year of the survey, marital status, migration background, household income, education and paid occupation, smoking status, alcohol use, #glasses of alcohol per week (except for depression), BMI, physical activity, neighbourhood level mean income and percentage non-western, and GGD-region. UFP expressed per 5,000 #/cm^3; EXC expressed per 100 hours per month.

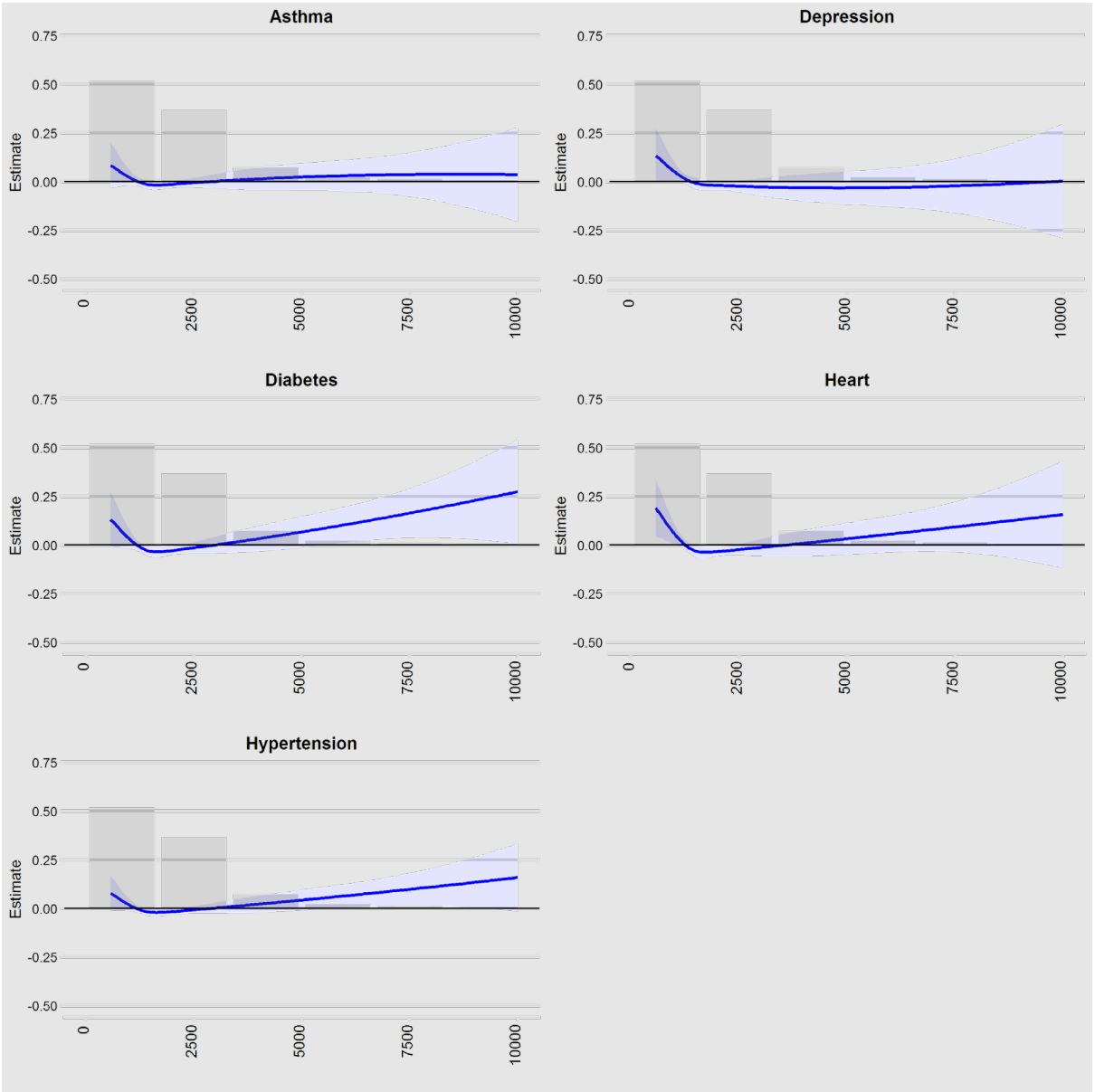


Figure 6.9 Natural cubic splines (3 df) for the association between UFP from aviation and prevalence of medication use. Shaded: 95% confidence interval. Histogram of exposure added to illustrate sparse data regions.

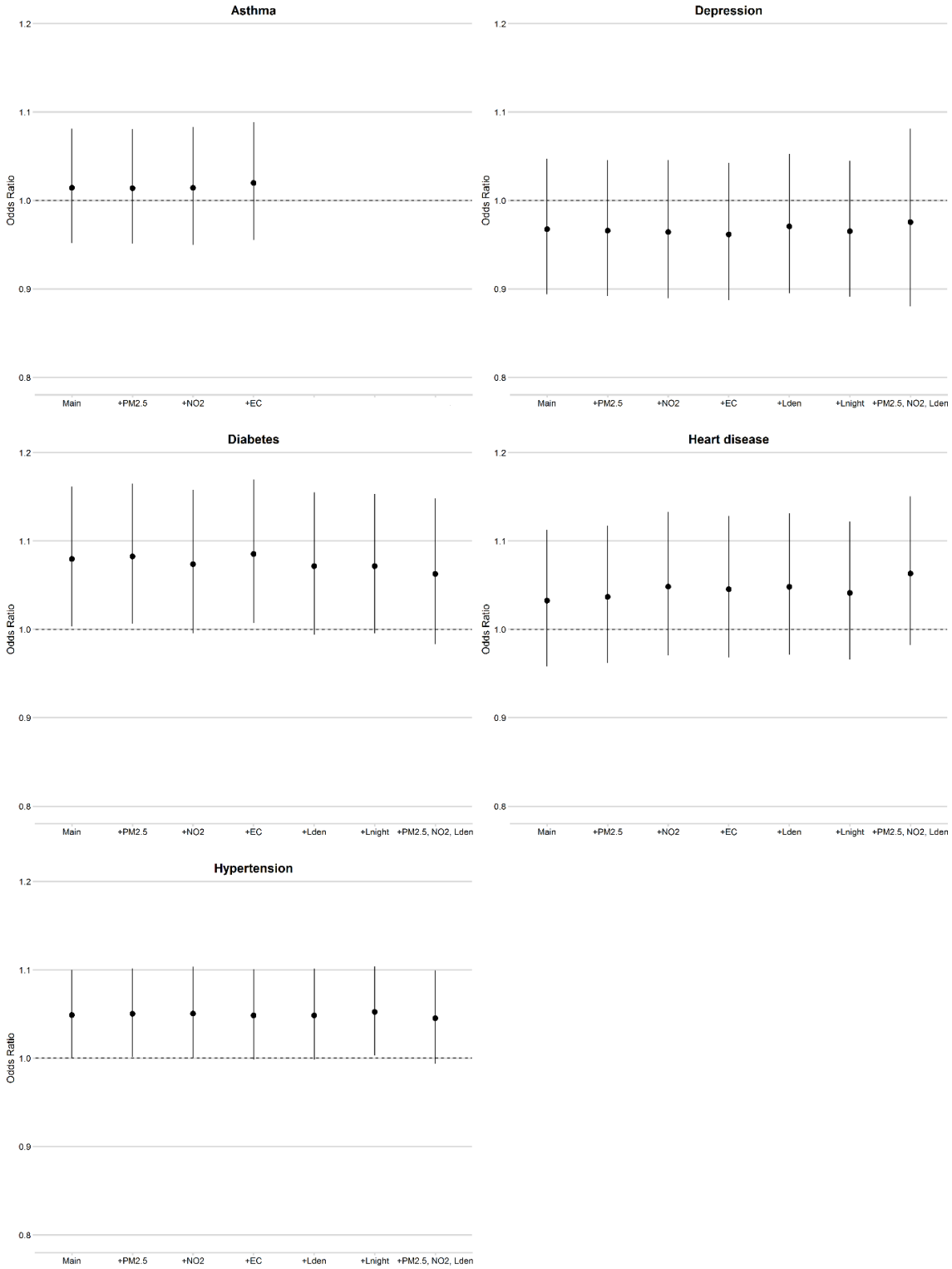


Figure 6.10 Associations between UFP from aviation after adjustment for co-pollutants and noise (Main: Main model (M4); +PM2.5: adjusted for PM2.5; +NO2: Adjusted for NO2; +EC: adjusted for EC; +Lden: adjusted for 24-h average noise from Schiphol, road traffic and rail traffic; +Lnight: adjusted for 8-h night-time noise from Schiphol, road traffic and rail traffic. All models adjusted for: see Figure 6.8. Effect estimates expressed per 3,500 #/cm^3.

6.3.5.2 Sensitivity analyses and stratifications

Results were generally robust in the different sensitivity analyses (figure 6.11). The significant association with diabetes persisted in all sensitivity analyses. The association with hypertension (p=0.051 in the main model) became statistically significant at the p<0,05 level in 5 out of the 8 sensitivity analyses.

Overall, results from the stratified analyses do not show much evidence for effect modification (figure 6.12). We observed some differences for diabetes, where the effect is driven by subjects living in non-urban areas; for hypertension, the effect is driven by the PHM 2012 and only statistically significant for men. For heart disease, we observed a significant association in men (OR 1.17 (95%CI 1.05-1.31)), while an inverse association is observed in women (OR 0.89 (95%CI 0.79-1.00)).

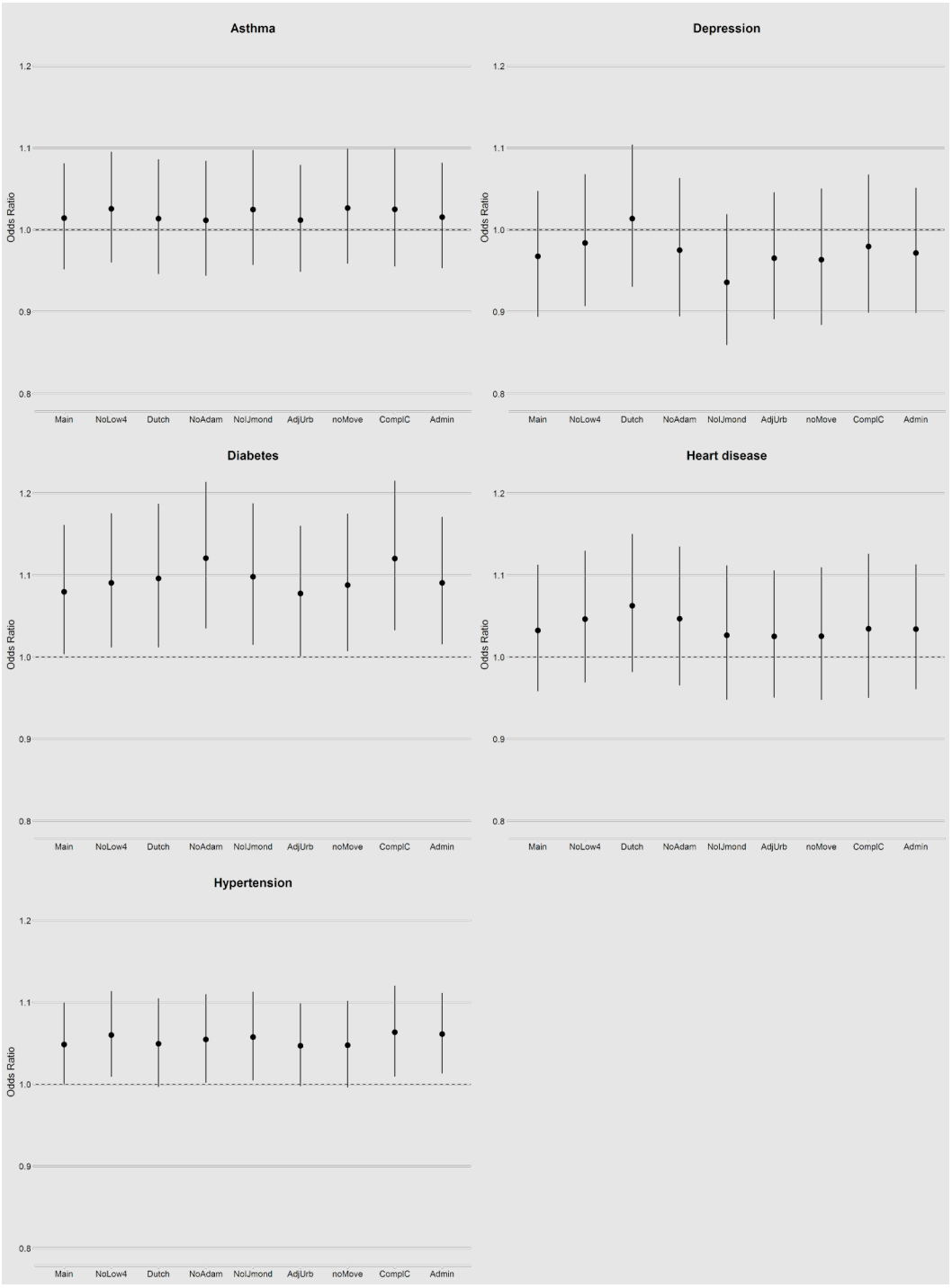


Figure 6.11 Associations between UFP from aviation and medication use in sensitivity analyses. Main, NoLow4, NoAdam, NoIJmond, noMove and ComplC adjusted for age, sex, year of the survey, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, BMI, physical activity, neighbourhood level mean income and percentage non-western and GGD-region; Dutch: same as main, except migration background (only 1 level); AdjUrb additionally adjusted for the degree of urbanisation (5 categories); Admin: Model adjusted for covariates available in the administrative records, i.e. age, sex, marital status, migration background, household income, neighbourhood level mean income and percentage non-western and GGD-region; Effect estimates expressed per 3,500 #/cm^3.

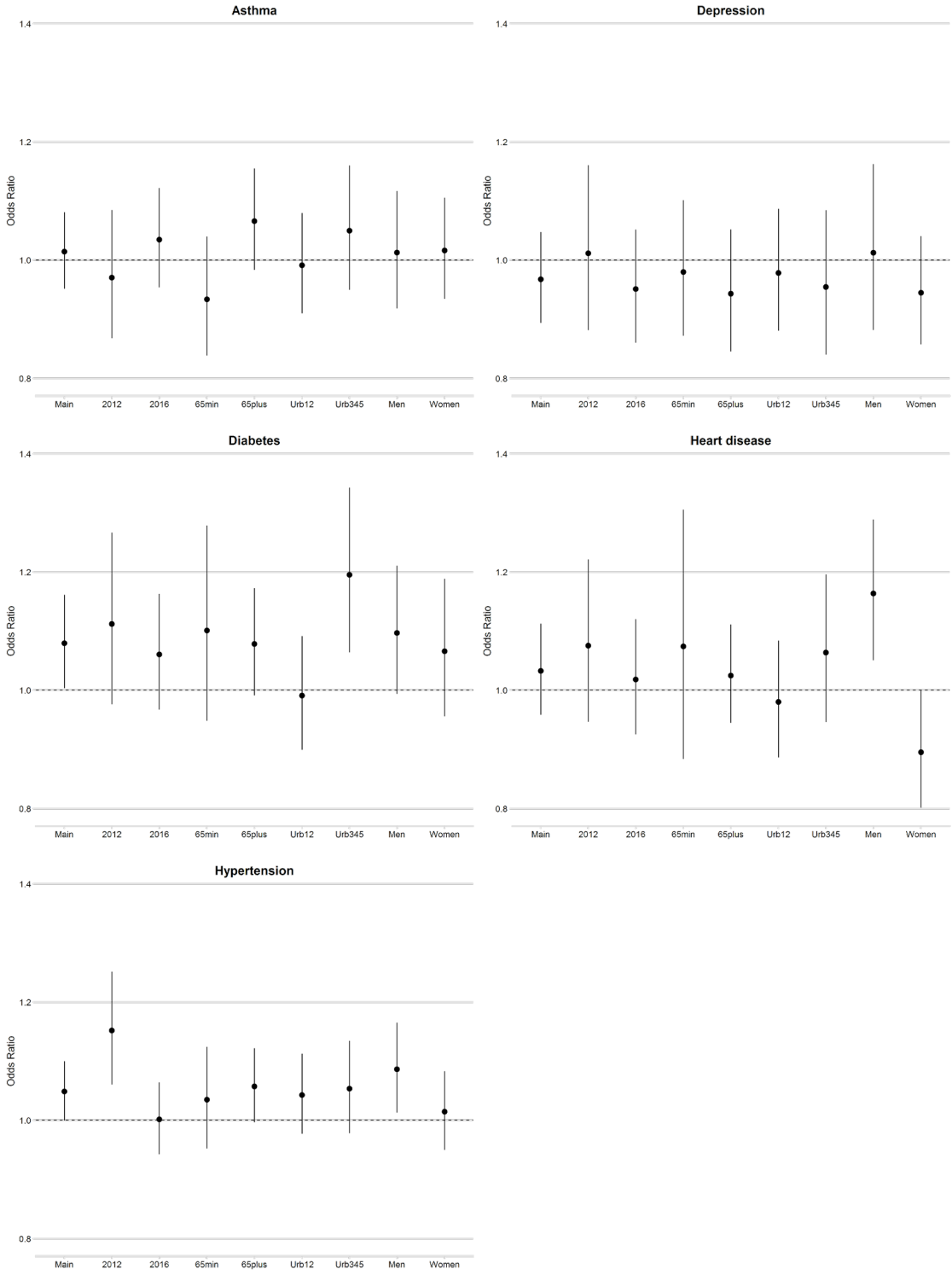


Figure 6.12 Associations between UFP from aviation and medication use in stratified analyses. All models adjusted for: see Figure 6.8; Effect estimates expressed per 3,500 #/cm^3.

6.3.6 Associations between UFP from aviation and self-reported disease

6.3.6.1 Main model

Figure 6.13 presents results from the different confounders models for the association between UFP from aviation and the prevalence of self-reported, physician treated, disease. These outcomes are only available for the PHM 2012.

Self-reported, physician treated, diabetes, hypertension and heart attack were all significantly associated with UFP from aviation. Stroke was significantly associated with UFP from aviation in models 1 to 3, but lost statistical significance after adjustment for GGD-region. In the main model (model 4) effect estimates for these outcomes ranged from OR=1.16 (95%CI 1.02-1.33) for diabetes to OR=1.39 (95%CI 1.17-1.67) for heart attack. We observed no significant associations between UFP and the other heart diseases or asthma.

Associations were similar for the other exposure specifications (figure 6.14) and other air pollutants and noise (figure 6.16).

Figure 6.15 shows concentration-response functions for UFP and self-reported, physician treated, diseases. As observed for psychological distress and medication use, we observed a decreasing trend at the lowest concentrations for all outcomes except hypertension. This pattern mostly disappeared when we excluded the 4 municipalities with the lowest UFP exposure (see appendix figure A6.1b).

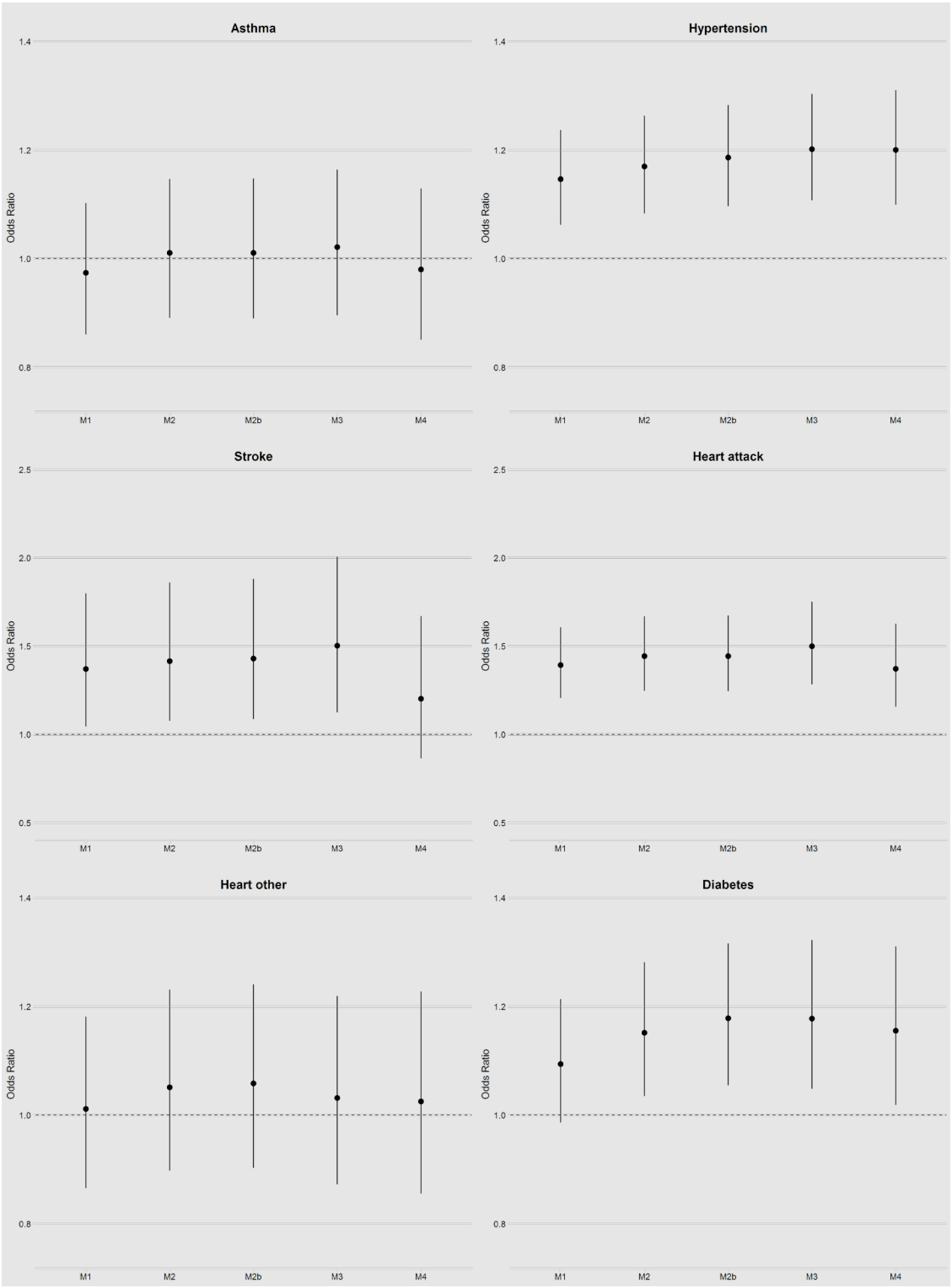


Figure 6.13 Associations between UFP from aviation and self-reported disease in different confounder models. (M1: adjusted for age & sex; M2: M1+ marital status, migration background, household income, education and paid occupation; M2b: M2 + smoking status #cigarettes smoked per day, alcohol use, #glasses of alcohol per week, BMI and physical activity; M3: M2b + neighbourhood level mean income and percentage non-western; M4: M3 + GGD-region. Effect estimates expressed per 3,500 #/cm^3 (Please note the different range on the Y-axis for heart attack and stroke).

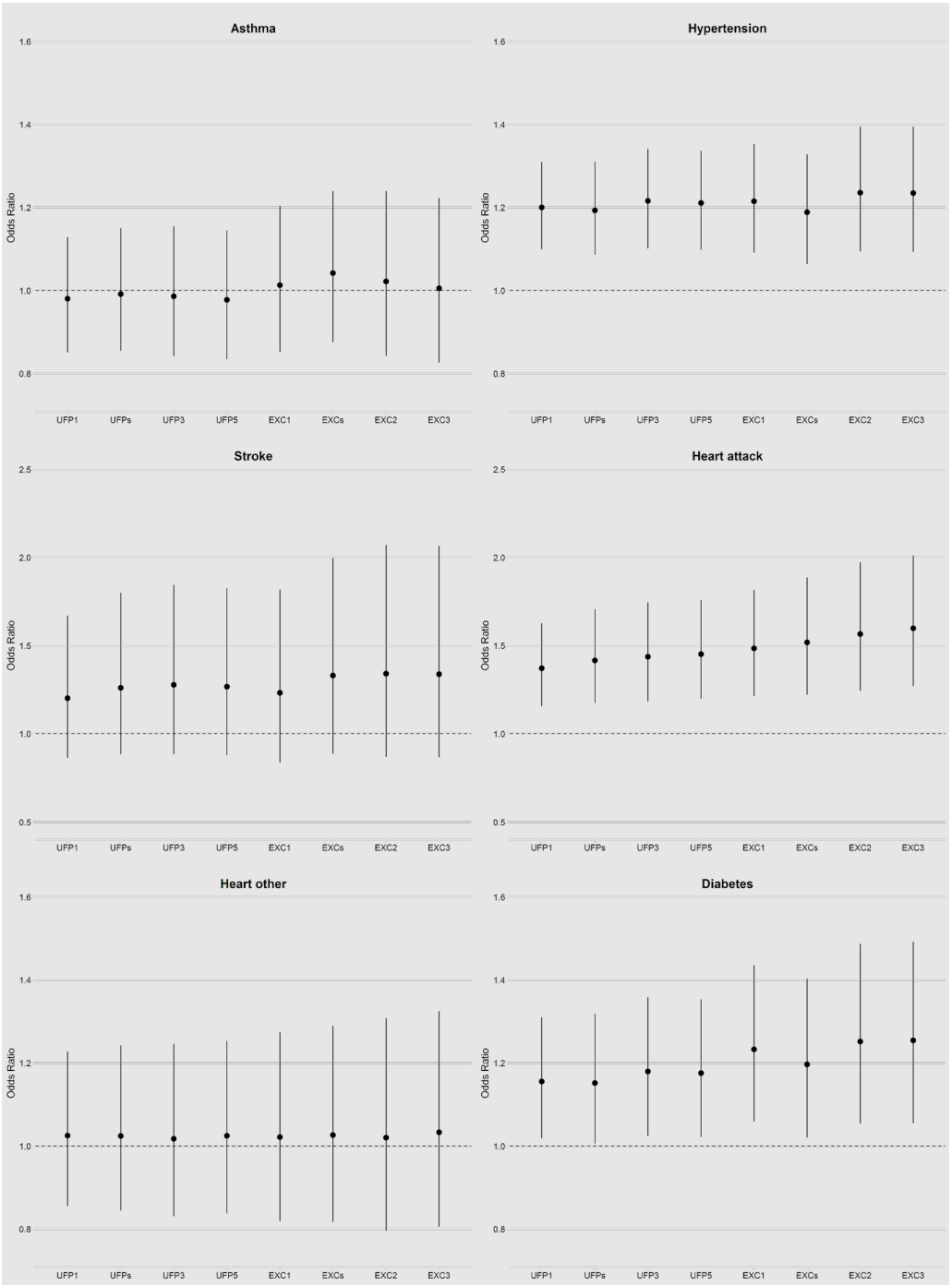


Figure 6.14 Associations between UFP from aviation and self-reported disease for different exposure variables. (UFP1: 1-year average exposure in the year of the survey; UFP1s: 1 year average exposure based on the 12 months before the survey (September 2012); UFP3: 3 year average exposure; UFP5: 5 year average exposure; EXC1: hours with peak exposure in the year of the survey; EXC1s: annual average based on the 12 months before the survey (September 2012); EXC3: 3 year average; EXC5: 5 year average). All models adjusted for age, sex, marital status, migration background, household income, education and paid occupation, smoking status, alcohol use, #glasses of alcohol per week, # cigarettes smoked per day, BMI, physical activity, neighbourhood level mean income, percentage non-western and GGD-region. UFP expressed per 3,500 #/cm3; EXC expressed per 100 hours per month.

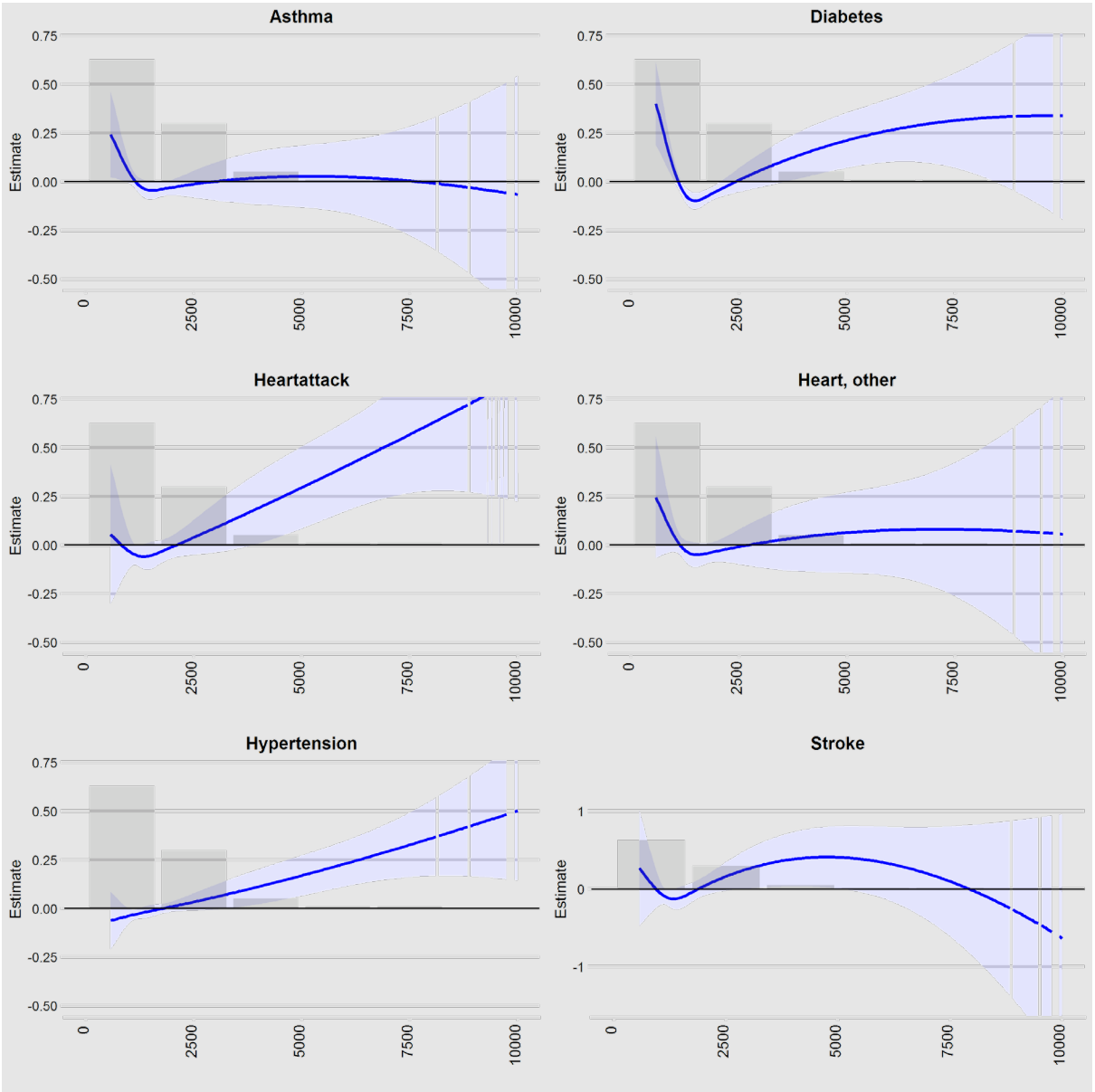


Figure 6.15 Natural cubic splines (3 df) for the association between UFP from aviation and prevalence of self-reported, physician treated disease. Shaded: 95% confidence interval. Histogram of exposure added to illustrate sparse data regions.

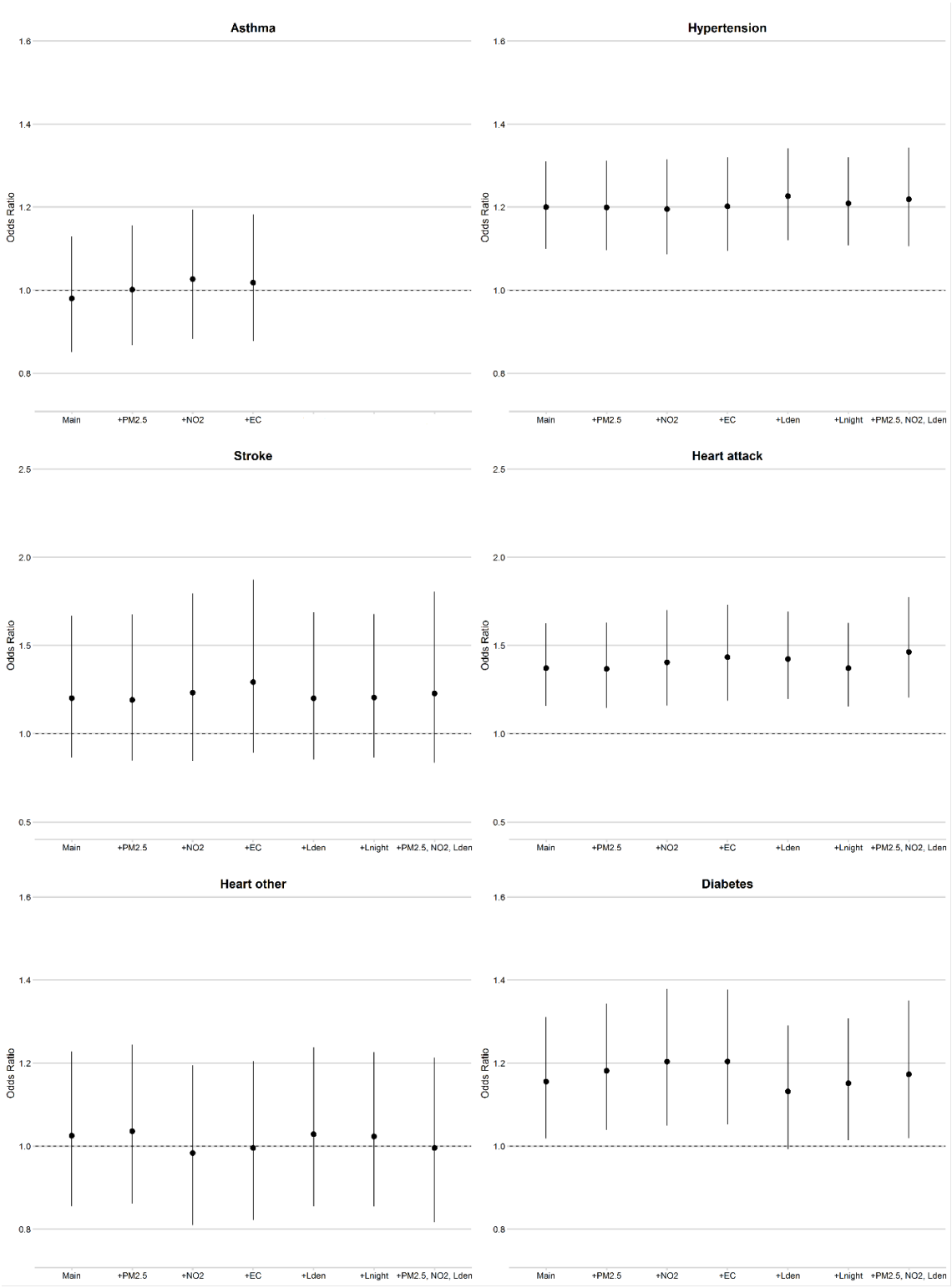


Figure 6.16 Associations between UFP from aviation and self-reported disease after adjustment for other air pollutants and noise (Main: Main model (M4); +PM2.5: adjusted for PM2.5; +NO2: Adjusted for NO2; +EC: adjusted for EC; +Lden: adjusted for 24-h average noise from Schiphol, road traffic and rail traffic; +Lnight: adjusted for 8-h nighttime noise from Schiphol, road traffic and rail traffic.). All models adjusted for: see Figure 6.14. UFP expressed per 3,500 #/cm^3.

6.3.6.2 Sensitivity analyses and stratifications

Results were robust in the different sensitivity analyses (figure 6.17). Generally, effect estimates increased when subjects from the four municipalities with the lowest average UFP exposure were excluded, or when subjects with imputed data were excluded (complete case analyses; n=29,981 out of 36,617).

In stratified analyses (figure 6.18), the effect on diabetes was restricted to subjects younger than 65 years and subjects living in less urbanized neighbourhoods. For the other outcomes (hypertension, heart attack, stroke, other heart disease and asthma) we observed no noteworthy differences.

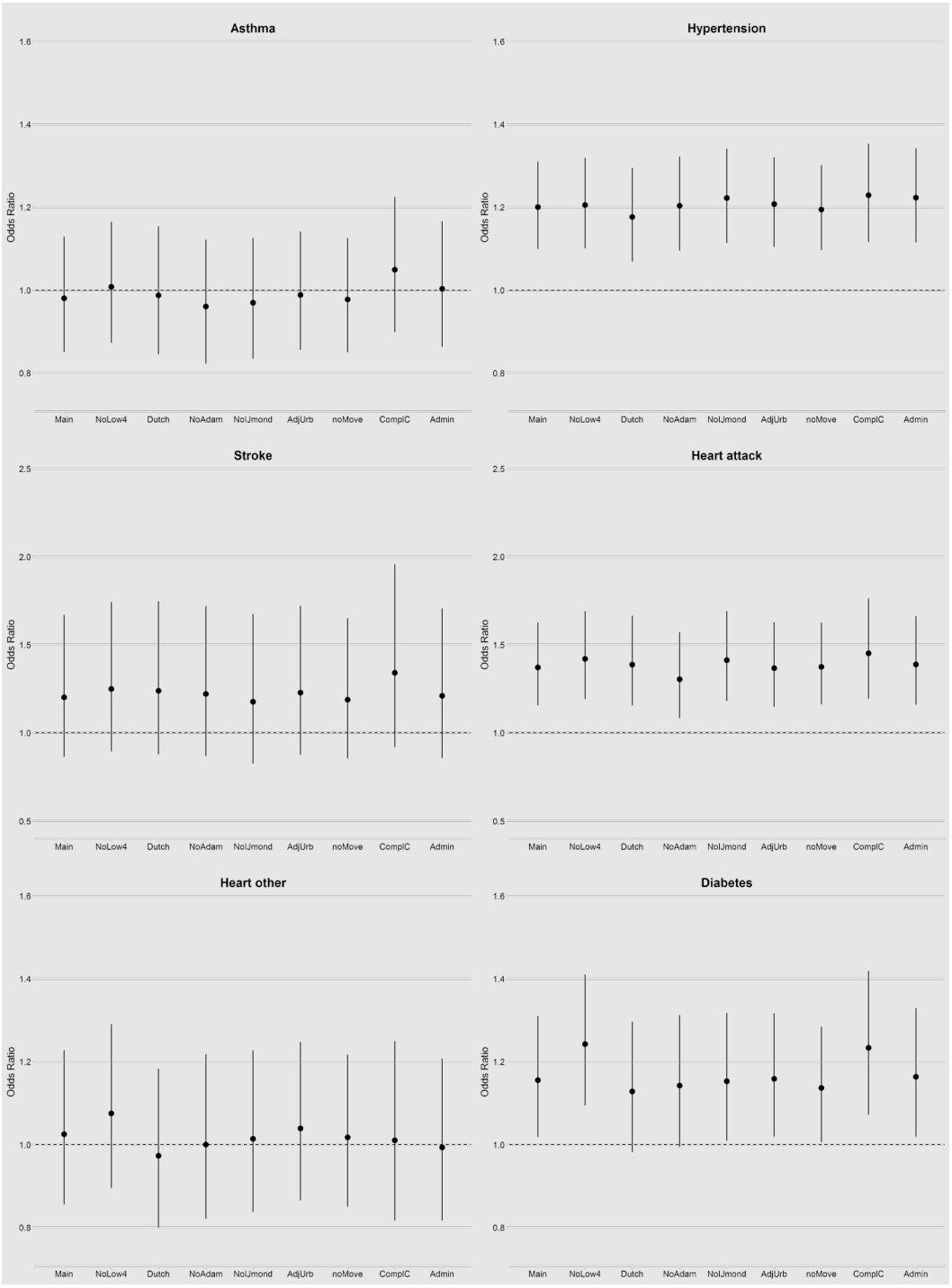


Figure 6.17 Associations between UFP from aviation and self-reported disease in sensitivity analyses. Main, NoAdam, NoIJmond, adjusted for age, sex, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, #glasses of alcohol per week, # of cigarettes smoked per day, BMI, physical activity, neighbourhood level mean income and percentage non-western; Dutch: same as main, except migration background (only 1 level; Admin: Model adjusted for covariates available in administrative record, i.e. age, sex, marital status, migration background, household income, neighbourhood level mean income and %non-western; ComplC: Complete case analyses. Effect estimates expressed per 3,500 #/cm^3.

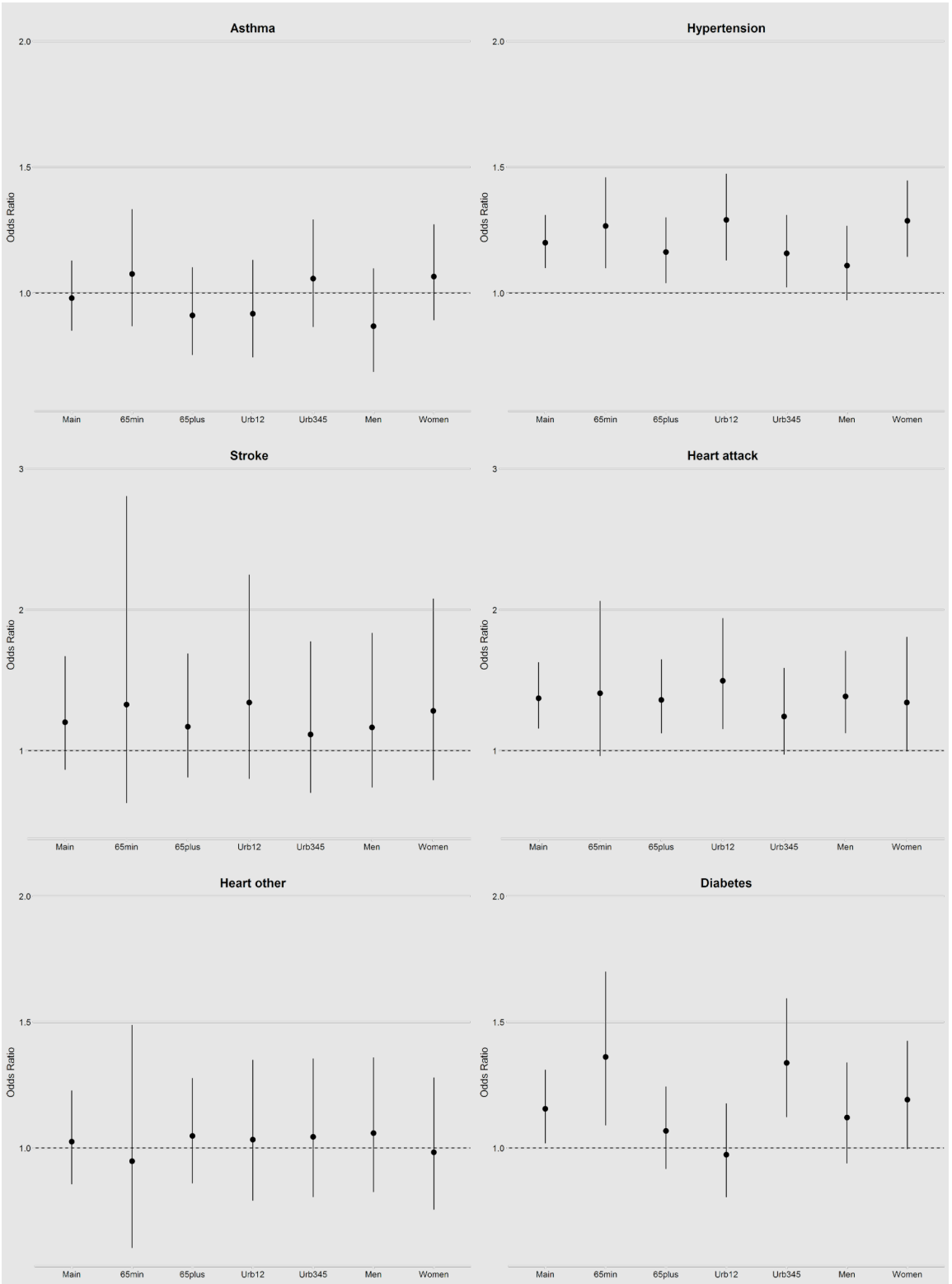


Figure 6.18 Associations between UFP from aviation and self-reported disease in stratified analyses. All models adjusted for age, sex, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, # glasses of alcohol per week, # of cigarettes smoked per day, BMI, physical activity, neighbourhood level mean income and percentage non-western and GGD-region; Effect estimates expressed per 3,500 #/cm^3.

6.3.6.3 Evaluation of potential residual confounding due to incomplete adjustment for lifestyle factors

Influence on associations for self-reported health and medication use
Table 6.8 compares effect estimates for UFP from aviation for the model in which only covariates are included that are available for the studies on mortality and medication use, being age, sex, marital status, migration background, household income, neighbourhood level mean income and %non-western (model "Admin" in figures 6.5, 6.11 and 6.17), with effect estimates from the further adjusted models, including education, paid occupation, smoking, alcohol consumption, BMI and physical activity. Effect estimates for the different models were very similar, suggesting very little confounding by these factors in this study.

Influence on associations for mortality
We analysed the association between UFP from aviation and natural mortality within the population of participants of the PHM 2012. In the main model we adjusted for age, sex, marital status, migration background, household income, education, paid occupation, smoking status, alcohol use, BMI, physical activity, neighbourhood level mean income, neighbourhood level percentage non-western, and GGD-region. We did not observe any association in the main model (Figure 6.19). When we selected covariates to match the mortality substudy (see 3.2.6.1), the associations remained essentially unchanged. Mortality risks in current smokers, obese subjects, and subjects <65 years were elevated, although with much wider confidence intervals that included unity. Associations in former smokers and overweight subjects changed direction, remaining statistically non-significant. Results of all other sensitivity analyses were essentially identical to the results of the main model, showing no association.

Results of the indirect adjustment are presented in chapter 3 (paragraph 3.3.4.3.2). After indirect adjustment, the HR for natural mortality increased slightly: from 0.990 (95% CI 0.971; 1.009) to 1.005 (95%CI 0.986; 1.025).

Table 6.8 Overview of effect estimates for UFP from aviation with increasing adjustment for individual confounders.

		Adjusted for confounders available in all registries		**Additional adjustment for education, paid occupation, smoking, alcohol use, BMI and physical activity**		**Additional adjustment for number of glasses of alcohol per week**		**Additional adjustment for number of cigarettes smoked per day[1]**	
		OR	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Primary outcomes	SPH	0.99	(0,89, 1.10)	0.99	(0.89, 1.11)	0.99	(0.89, 1.11)		NA
	Distress	0.96	(0,86, 1.06)	0.95	(0.85, 1.05)	0.95	(0.85, 1.05)		NA
Medication use	Depression	0.97	(0.89, 1.05)	0,97	(0.89, 1.05)	0.97	(0.89, 1.05)		NA
	Diabetes	**1.10**	(**1.02**, **1.18**)	**1,08**	(**1.01**, **1.17**)	**1.08**	(**1.00**, **1.17**)		NA
	Hypertension	**1.06**	(**1.01**, **1.12**)	**1,05**	(**1.00**, **1.11**)	1.05	(1.00, 1.11)		NA
	Heart disease	1.04	(0.96, 1.12)	1,03	(0.96, 1.12)	1.03	(0.96, 1.12)		NA
	Asthma	1.02	(0.95, 1.09)	1,02	(0.95, 1.09)	1.02	(0.95, 1.09)		NA
Self-reported, physician treated 2012[1]	Diabetes	**1.14**	(**1.01**, **1.30**)	**1,17**	(**1.02**, **1.33**)	**1.17**	(**1.02**, **1.33**)	**1.16**	(**1.02**, **1.33**)
	Stroke	1.20	(0.85, 1.69)	1,22	(0.87, 1.73)	1.21	(0.86, 1.72)	1.21	(0.86, 1.71)
	Hypertension	**1.21**	(**1.10**, **1.32**)	**1,21**	(**1.10**, **1.33**)	**1.21**	(**1.10**, **1.33**)	**1.21**	(**1.10**, **1.33**)
	Heart attack	**1.40**	(**1.17**, **1.67**)	**1,40**	(**1.17**, **1.67**)	**1.39**	(**1.17**, **1.67**)	**1.39**	(**1.17**, **1.67**)
	Heart, other	1.02	(0.84, 1.23)	1,03	(0.85, 1.24)	1.02	(0.85, 1.24)	1.03	(0.85, 1.24)
	Asthma	0.98	(0.84, 1.13)	0,98	(0.84, 1.14)	0.98	(0.84, 1.14)	0.98	(0.84, 1.14)

[1] Only available for 2012.

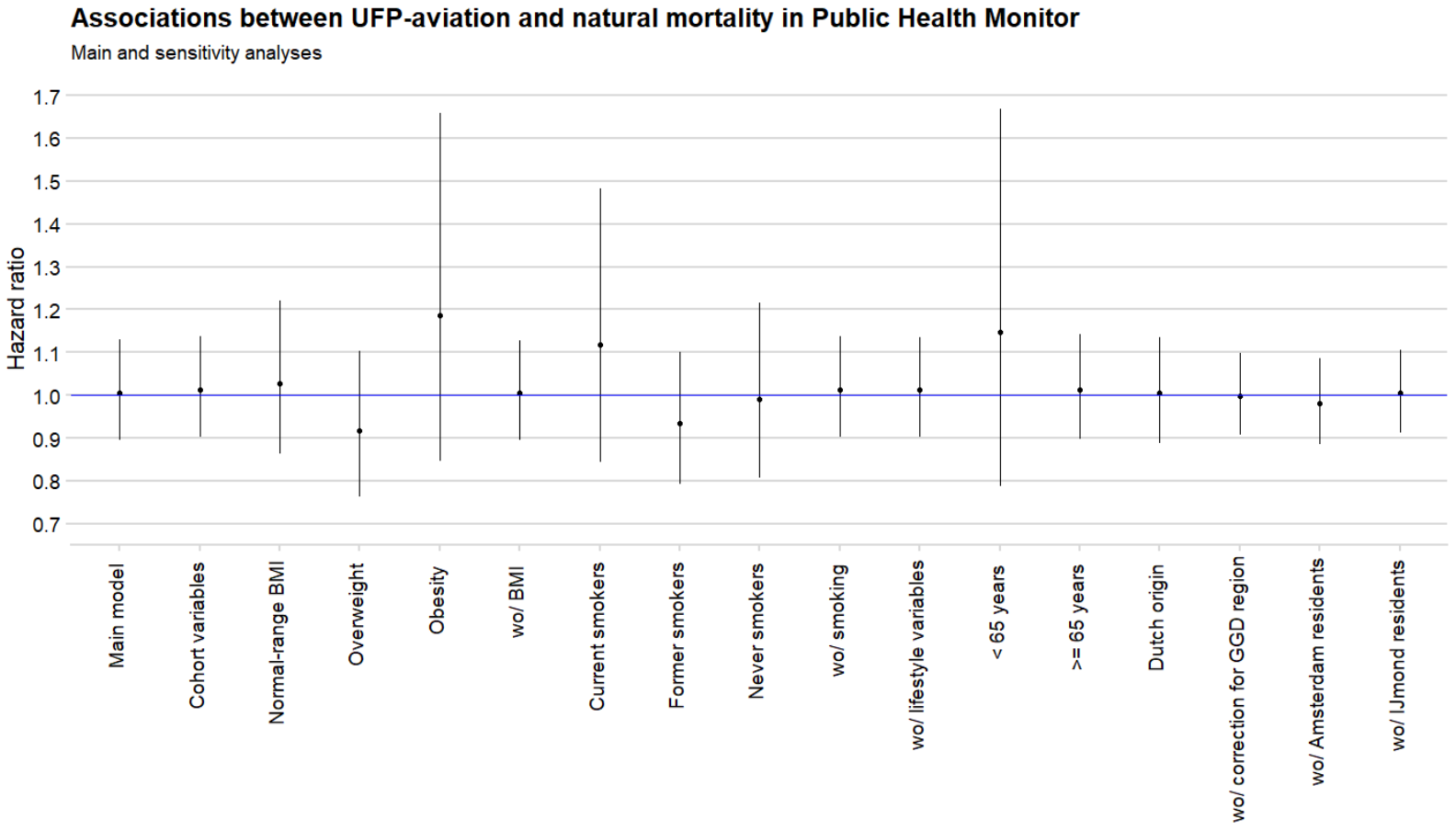


Figure 6.19 Association between UFP-aviation and natural mortality in Public Health Monitor. N = 29,851. HR expressed per 3,500 #/cm^3 increase in UFP.

Associations between UFP from aviation and lifestyle variables
Table 6.9 presents the associations between lifestyle factors (smoking status, BMI, alcohol use and physical activity) with exposure to UFP from aviation within the stratified sample of participants of the PHM with similar distributions of covariates as the mortality cohort (n=3,333; see 3.3.4.3.1).

Table 6.9 Associations between UFP from aviation and lifestyle variables in the stratified PHM sample with similar distributions of covariates as the mortality cohort (n=3,333). Estimates express the difference in #/cm^3 compared to the reference category.

Model	Lifestyle variable	Level	Estimate (SE)
Smoking only	Smoking	Current	-61 (59)
		Former	34 (51)
BMI only	BMI*	Underweight	-32 (237)
		Overweight	119 (49)
		Obese	41 (67)
Alcohol only	Alcohol consumption	Current	-69 (72)
		Former	-103 (106)
Physical activity only	Physical activity**	≤180 min/week	-57 (65)
		180-480 min/week	-73 (63)
		480-1050 min/week	-5 (61)
Smoking + BMI	Smoking	Current	-56 (59)
		Former	33 (51)
	BMI*	Underweight	-22 (237)
		Overweight	115 (49)
		Obese	36 (67)
Smoking + BMI + alcohol + physical activity	Smoking	Current	-52 (59)
		Former	43 (51)
	BMI*	Underweight	-21 (237)
		Overweight	111 (49)
		Obese	29 (68)
	Alcohol consumption	Current	-63 (73)
		Former	-94 (107)
	Physical activity**	≤180 min/week	-58 (65)
		180-480 min/week	-74 (63)
		480-1050 min/week	-7 (62)

* According to WHO classification: underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese (≥ 30 kg/m^2).
** Physical activity: categorized as quartiles from the distribution for all participants.
Reference levels: never smokers, normal-weight BMI, never drinkers, high physical activity (>1050 min/week). Model: UFP-aviation = lifestyle variables + age + sex + marital status + migration background + household income + neighbourhood-level income + percentage of inhabitants with non-western migration background + percentage of inhabitants with low education.

Current smoking, alcohol consumption and low physical activity were associated with somewhat lower exposure to UFP from aviation, while overweight and obesity were associated with higher exposure to UFP from aviation. With the exception of overweight, none of these differences were statistically significant.

Table 6.10 compares the distribution of covariates in the dataset, including all mother-infant pairs (n=287,167), the stratified sample of female participants of the PHM with similar distributions for age, migration background and education (n=3,064) and for participants who were pregnant at the survey date (n=550), as well as the distribution of smoking, alcohol use, BMI and physical activity in the two samples. The group of pregnant women that participated in the PHM included more women of Dutch origin and more highly educated women compared to all mothers and the stratified sample. Also, this group included less current smokers (10.5% compared to 22.7% in the stratified sample) and more former smokers and alcohol users, suggesting that some women may have changed their smoking and/or drinking habits during pregnancy.

Table 6.11 presents the associations between lifestyle factors (smoking status, BMI, alcohol use and physical activity) with exposure to UFP from aviation within the two groups. In both samples smoking, alcohol consumption and overweight/obesity were generally associated with lower exposure to UFP from aviation. Effect estimates in the group of pregnant women were generally higher than for the stratified sample, but with (much) larger standard errors, probably related to the small sample size. In the stratified sample, the differences between current alcohol consumers and never drinkers (-130 #/cm^3) and between obese women compared to women of normal weight (-170 #/cm^3) were statistically significant.

Table 6.10 Characteristics of the stratified sample and pregnant women that participated in the PHM.

	All mothers (n=287,167) %	Stratified sample PHM (n=3064) %	Pregnant women in PHM (n=550) %
Age			
≤ 19	0.8	0.8	
20-29	24.7	24.6	24.7
30-34	38.7	38.7	44.7
35-39	31.1	31.1	26.9
≥40	4.8	4.8	3.6
Marital Status			
Married/living together	54.0	56.6	53.5
Unmarried/never married	42.8	39.6	44.7
Divorced/widowed	3.2	3.8	1.8
Migration background			
Dutch	57.5	57.5	71.8
Other	42.5	42.5	28.2
Maternal education			
Low	18.6	18.6	11.6
Medium	30.2	30.1	30.2
High	51.2	51.3	58.2
Smoking			
Current		22.7	10.5
Former		22.6	34.0
Never		54.7	55.5
Alcohol use			
Current		77.1	72.9
Former		5.2	13.1
Never		17.8	14.0
BMI			
Normal weight		63.1	68.4
Overweight		24.4	22.0
Obese		9.1	8.2
Physical activity			
≤ 180 min/week		22.6	26.5
180-480 min/week		29.4	31.8
480-1050 min/week		22.6	19.3
>1050 min/week		25.4	22.4

Table 6.11 Associations between UFP from aviation and lifestyle variables in the stratified PHM sample with similar distributions of covariates as the women in the study on pregnancy outcome (n=3,064) and in participants who were pregnant at the date of the survey (n=550). Estimates express the difference in #/cm^3 compared to the reference category.

Model	Variable	Level	Stratified sample PHM (n=3064)	Pregnant women in PHM (n=550)
			Estimate (SE)	Estimate (SE)
Smoking only	Smoking	Current	-23 (57)	-105 (189)
		Former	-67 (55)	12 (131)
Alcohol only	Alcohol consumption	Current	-131 (66)*	-253 (205)
		Former	-102 (112)	-143 (245)
BMI only	BMI	Overweight	-33 (53)	-157 (143)
		Obese	-167 (80)*	-257 (222)
Physical activity only	Physical activity	≤180 min/week	14 (65)	125 (172)
		180-480 min/week	45 (61)	91 (167)
		480-1050 min/week	-57 (64)	92 (181)
All four	Smoking	Current	-4 (57)	-55 (199)
		Former	-50 (57)	53 (133)
	Alcohol consumption	Current	-132 (68)#	-281 (209)
		Former	-87 (113)	-141 (246)
	BMI	Overweight	-39 (53)	-171 (144)
		Obese	-174 (80)*	-277 (223)
	Physical activity	≤180 min/week	15 (65)	88 (174)
		180-480 min/week	45 (61)	66 (168)
		480-1050 min/week	-56 (64)	75 (183)

* p<0.05; # p<0.10 (compared to reference)
Physical activity: categorized as quartiles from the distribution for all participants.
Reference levels: never smokers, normal weight BMI, never drinkers, high physical activity (>1050 min/week). Model: UFP-aviation = lifestyle variables + age + marital status + migration background + education + household income + neighbourhood-level percentage of inhabitants with non-western migration background + percentage of inhabitants with high education.

6.4 Main findings

6.4.1 *Summary and classification*

Table 6.12 presents a summary of the results in the main model and the overall classification of the different outcomes, organized by type of effect.

Table 6.12 Summary of results in the main model and classification of the association, organized by organ system (n=90,880 for primary outcomes and medication use; n=36,617 for self-reported, physician treated disease; primary outcomes in bold). OR expressed per 3,500 #/cm^3.

Outcome	OR	(95% CI)	Classification
General			
Self-perceived health	**0.99**	**(0.89, 1.11)**	**No association**
Respiratory			
Asthma (medication)	1.02	(0.95, 1.09)	No association
Asthma (self-reported)[1]	0.98	(0.84, 1.14)	No association
Cardiovascular			
Heart disease (medication)	1.03	(0.96, 1.12)	Possible association
Hypertension (medication)	1.05	(1.00, 1.11)	Clear association
Hypertension (self-reported)[1]	1.21	(1.10, 1.33)	Clear association
Heart attack (self-reported)[1]	1.39	(1.17, 1.67)	Clear association
Stroke (self-reported)[1]	1.21	(0.86, 1.71)	Possible association
Other heart disorder (self-reported)[1]	1.03	(0.86, 1.24)	No association
Metabolic			
Diabetes (medication)	1.08	(1.00, 1.17)	Clear association
Diabetes (self-reported)[1]	1.16	(1.02, 1.33)	Clear association
Mental health			
Psychological distress	**0.95**	**(0.85, 1.05)**	**No association**
Depression (medication)	0.97	(0.89, 1.05)	No association

[1] 2012 only.

6.4.2 *Rationale for the classification*

- We classified associations for endpoints related to **general health (self-perceived health), respiratory disease (asthma)** and **mental health (psychological distress and use of antidepressants)** as **''no association''**. These associations were all non-significant in the main models and did not show a clear consistent pattern of elevated (or reduced) risks across all sensitivity analyses. For the mental health outcomes, associations were generally below unity. However, this association only reached statistical significance for psychological distress when the population was restricted to subjects of Dutch origin, while the association for use of antidepressants was (slightly) above unity in that population.

- For endpoints related to **cardiovascular disease**, we found a significant association with **hypertension** (based on prescribed medication as well as on self-report) and self-reported, physician treated **heart attack**. These associations persisted after adjustment for co-pollutants as well as in sensitivity analyses. The associations with medication use for hypertension were driven by 2012 (OR 1.16 (95%CI 1.06-1.27), which is more similar to the association found with self-reported hypertension). However, for outcomes available in both years we put most weight on the associations in the combined dataset, which were robust across all sensitivity analyses and other strata. We therefore classified associations with heart attack and hypertension as **''clear associations''**.
  Effect estimates for medication for **heart disease** and self-reported **stroke** were consistently elevated, but did not reach statistical significance in any of the models. The only exception was the stratified analyses by gender for medication for heart disease, where we observed a significant positive association in men (OR 1.17 (95%CI 1.05-1.31)) and an inverse association in women (OR 0.89 (95%CI 0.79-1.00)). We therefore classified associations with medication for heart disease and self-reported stroke as **''possible association''.** For **metabolic disease, diabetes** was significantly associated with UFP from aviation, based on both medication use (2012 & 2016) and self-reported, physician treated (only available for 2012). These associations persisted after adjustment for co-pollutants as well as in sensitivity analysis. In stratified analyses, the association was not observed for subjects living in urban areas, but was robust across all other strata. We therefore classified associations with diabetes as **''clear associations''**.

Further interpretation of the observed associations is described in chapter 7.

6.4.3 Study specific aspects

6.4.3.1 Introduction

In this section we describe methodological aspects that are specific to the study presented in this chapter. More general aspects that apply to the study as a whole, such as exposure classification and adjustment for other air pollutants and noise, are addressed in chapter 7.

6.4.3.2 Classification of health outcomes

Primary outcomes

Both primary outcomes were based on self-report, which may result in outcome misclassification. Psychological distress was based on the Kessler psychological distress scale (K10) (Kessler et al. 2002). The K10 is based on ten questions about anxiety and symptoms of depression experienced during the preceding four weeks. Andrews & Slade (Andrews and Slade 2001) showed a significant association between the outcomes of the K10 and the number of consultations for a mental problem in the preceding twelve months. Moreover, they showed a clear relation between scores on the K10 and scores on the General Health Questionnaire and the 12-Item Short Form Health Survey (both

measured with respect to the last 30 days), measures of symptoms and disability respectively (Andrews and Slade 2001).

Self-perceived general health (SPH) is considered a comprehensive and sensitive indicator of an individual's health status, which is commonly used in epidemiological studies. It has been shown to be a strong predictor of hospitalisation and mortality (Benyamini 2011; Nielsen 2016; Idler and Benyamini 1997). Questions on SPH and distress were identical in both years.

Secondary outcomes
Classification of these health outcomes was either based on self-report (questionnaire) or on registered prescribed medication. Details and discussion on the classification of health outcomes based on medication use are described in paragraph 5.4.3.2, with the main difference that we studied prevalence in the health monitor instead of incidence.

Self-reports from questionnaires have been found to agree moderately to very well with medical records for **diabetes, hypertension, asthma and heart attack,** with kappa coefficients ranging from 0.76 to 0.94 for diabetes, from 0.54 to 0.75 for hypertension, 0.61 to 0.70 for asthma and from 0.48 to 0.80 for heart attack (Okura et al. 2004; Tisnado et al, 2006; Leikauf et al, 2009; Schneider et al. 2012; Hansen et al. 2014; Muggah et al. 2013; Machón et al. 2013). Agreements for **stroke** varied more widely between studies, with kappa statistics ranging from 0.35 to 0.71 (Okura et al. 2004; Schneider et al. 2012; Muggah et al. 2013; Machón et al. 2013; Hansen et al. 2014).

For some of the outcomes information was available from both self-report (2012 only) as well as registered prescribed medication. Kappa coefficients for these outcomes were also high for diabetes (K=0.90) and moderate for asthma/COPD ((K=0.63) and hypertension (K=0.66) (see table A6.2). Effects estimates using self-report were similar to those based on the registered prescribed medication in the 2012 PHM, especially for asthma (OR 0.97 (95% CI 0.86; 1.09) and OR 0.98 (95% CI 0.84; 1.14)) and hypertension (OR 1.16 (95% CI 1.06; 1.27) and OR 1.21 (95% CI 1.10; 1.33)). For diabetes, the association was somewhat stronger and more precise for self-reported diabetes (OR 1.16 (95% CI 1.02; 1.33; p=0.02) compared to prescribed medication (OR 1.12 (95% CI 0.97; 1.28; p=0.11).

No distinction could be made between asthma and COPD, neither based on the medication data nor on the questionnaire data.

6.4.4 *Exposure-response functions*

Exposure-response curves generally confirmed the observations from the linear logistic regression models. For most outcomes we observed a decreasing trend at the lowest concentrations, with the strongest deviation from linearity observed for diabetes and heart disease medication. For all outcomes except heart disease medication, this pattern was no longer present when the four municipalities with the lowest UFP exposure were excluded. However, exclusion of these four municipalities had no substantial effect on the effect estimate. The largest change was observed for self-reported diabetes, for which the

effect estimate changed from 1.16 (95%CI 1.02-1.33) to 1.26 (95%CI 1.10-1.44).

6.4.4.1 Strengths and limitations

In addition to the use of self-reported health outcomes, which is discussed in paragraph 6.4.3.2, another limitation of this study is the cross-sectional study design, evaluating prevalence of the health outcomes instead of incidence. We had no information about the onset of the health outcomes, and hence we do not know whether the exposure preceded the health outcomes. The biologically most relevant time period between exposure to environmental factors and the onset of health outcomes is not well known. We evaluated different exposure windows, ranging from one to five-year average exposure, incorporating residential history in this five-year period. One to five-year average exposures were highly correlated (R>0.9), and effect estimates for the different exposure windows were very similar. Also, subjects may have moved after their disease developed. However, excluding subjects who had moved in the five years before the survey had no noteworthy impact on the effect estimates for any of the health outcomes.

An important strength of this study is the availability of information on lifestyle factors (e.g. smoking, alcohol use, BMI and physical activity), allowing for more complete adjustment for confounders compared to the studies on mortality, medication incidence and pregnancy outcomes. Effect estimates for models including education, paid occupation and lifestyle factors (smoking, alcohol consumption, BMI and physical activity) were very similar to effect estimates from models including only covariates from administrative databases, suggesting very little confounding by these factors in this study. Indirect adjustment for smoking status and BMI of association with natural mortality, using a randomly stratified sample of the PHM 2012 and 2016 with distribution of covariates (age, sex, marital status, migration background, household income) similar to the study population in the mortality study, confirmed this finding.

For further interpretation of potential bias, we used the PHM to provide insight in potential differences in UFP exposure for among others current smokers compared to never smokers and obese people compared to normal weight people in different subsamples of the PHM. Unfavourable lifestyle factors were generally associated with lower exposure to UFP from aviation. This suggests that not adjusting for these factors could have resulted in an underestimation of the effect, especially for pregnancy outcomes, for which we observed the biggest differences. However, this should be interpreted with care, as differences were largely non-significant, possibly related to the small sample size.

6.5 Appendix

Appendix A6.1 Characteristic of the study population in the imputed dataset compared to the complete case dataset.

Tables A6.1a&b include the distributions for the complete cases for the individual covariates that we used in the analyses of the primary

outcomes. Distributions for complete cases including glasses of alcohol per week and number of cigarettes smoked per day were similar.

Table A6.1a Characteristics of the study population in the imputed dataset compared to the complete case dataset: individual covariates.

	2012		**2016**	
	All subjects[1] (n=36,617) %	Complete case (n=31,769) %	All subjects[1] (n=54,263) %	Complete case (n=46,712) %
Sex: Male	44.5	45.0	44.7	45.2
Age[2]				
19-39	21.1	21.9	16.4	16.8
40-64	39.9	41.7	31.7	33.3
≥65	39.1	36.4	51.9	49.9
Marital status				
Married/living together	57.2	58.0	56.5	57.3
Unmarried/never married	23.8	24.6	21.4	22.0
Divorced	9.8	9.6	11.2	11.1
Widowed	9.2	7.8	10.9	9.7
Migration background				
Dutch	82.3	82.8	82.2	82.8
Netherlands Antilles	0.4	0.4	0.5	0.4
Surinam	2.1	2.0	1.9	1.8
Turkey	1.6	1.5	1.1	1.0
Morocco	1.3	1.2	0.8	0.7
Other, western	9.6	9.5	10.5	10.5
Other, non-western	2.7	2.6	3.1	2.8
Education				
Low	40.6	37.8	38.1	35.6
Medium	28.9	29.5	29.5	30.0
High	30.5	32.6	32.4	34.4
Household income[2]				
≤ 1 percentile	0.3	0.3	0.3	0.3
2-5 percentile	1.4	1.4	1.2	1.2
5-10 percentile	2.2	2.1	2.3	2.1
10-25 percentile	10.5	9.4	11.6	10.4
25-50 percentile	23.4	22.0	25.4	24.1
50-75 percentile	28.1	28.6	26.3	26.9
75-90 percentile	19.3	20.3	18.3	19.2
90-95 percentile	7.3	7.8	7.1	7.7
95-99 percentile	6.1	6.6	6.0	6.5
>99 percentile	1.4	1.5	1.4	1.5

[1] In the imputed dataset.
[2] Included in the analyses in 12 categories.

Table A6.1b Characteristics of the study population in the imputed dataset compared to the complete case dataset: Individual covariates, not available in any of the other sub-studies.

	2012		2016	
	All subjects[1] (n=36,617) %	Complete case (n=31,769) %	All subjects[1] (n=54,263) %	Complete case (n=46,712) %
Smoking status				
Current	19.9	19.8	16.7	16.6
Former	37.5	37.6	41.3	41.5
Never	42.6	42.6	42.0	41.9
# cigarettes smoked for current smokers (mean (sd))	11.2 (8.1)	11.2 (8.0)	N.A.	N.A.
Alcohol use				
Current	83.3	84.5	83.3	84.5
Former	5.5	5.2	6.2	5.8
Never	11.2	10.3	10.6	9.7
# of alcohol glasses/week for current consumers (mean (SD))	8.9 (9.7)	8.9 (9.7)	8.7 (9.7)	8.8 (9.6)
BMI				
< 18.5 kg/m^2	1.3	1.3	1.5	1.5
18.5-24.9 kg/m^2	47.4	48.1	46.6	37.8
25.0-30.0 kg/m^2	38.1	37.8	37.9	13.6
>30 kg/m^2	13.2	12.8	14.0	47.1
Physical activity				
≤180 min/week	28.2	27.1	23.5	21.8
180 – 480 min/week	27.4	27.7	24.7	25.2
480 – 1050 min/week	22.3	22.7	25.3	26.0
>1050 min/week	22.1	22.6	26.5	27.0
Paid occupation				
Yes	50.6	52.0	41.8	43.8
No	49.4	48.0	58.2	56.2

[1] In the imputed dataset.

Table A6.1c Prevalence of self-reported health outcomes in the imputed dataset compared to the complete case dataset (primary outcomes in bold).

	2012		**2016**	
Primary outcomes	All subjects[1] (n=36,617) N (%)	Complete case (n=31,769) N (%)	All subjects[1] (n=54,263) N (%)	Complete case (n=46,712) N (%)
Self-perceived poor general health	**1,416 (3,9)**	**1,118 (3,5)**	**2,607 (4,8)**	**1,999 (4,4)**
Severe psychological distress	**1,631 (4,6)**	**1,321 (4,2)**	**2,769 (5,1)**	**2,183 (4,8)**
Secondary outcomes				
Diabetes	2,841 (8.0%)	2,295 (7.3%)	NA	
Hypertension	7,082 (21.0%)	6,062 (20.2%)	NA	
Stroke	263 (0.7%)	200 (0.6%)	NA	
Heart attack	1,053 (3.0%)	832 (2.6%)	NA	
Other severe heart disorder	1,223 (3.4%)	958 (3.0%)	NA	
Asthma or COPD	2,232 (6.6%)	1,881 (6.2%)	NA	
Population ≥40	N=28,906	N=24,816		
Stroke	259 (0.9%)	198 (0.8%)		
Heart attack	1,040 (3.7%)	821 (3.4%)		
Other severe heart disorder	1,199 (4.3%)	936 (3.8%)		

[1] In the imputed dataset.

Table A6.1d Prevalence of medication use for medication groups in the imputed dataset compared to the complete case dataset[1].

	2012		**2016**	
	All subjects (n=36,617) N (%)	Complete case (n=31,769) N (%)	All subjects (n=54,263) N (%)	Complete case (n=46,712) N (%)
Diabetes	2,774 (7.6%)	2,194 (6.7%)	4,679 (8.6%)	3,818 (8.2%)
Hypertension	11,587 (31.6%)	9,478 (29.8%)	19,449 (35.8%)	16,085 (34.4%)
Heart disease	2,744 (7.5%)	2,095 (6.6%)	4,573 (8.4%)	3,615 (7.7%)
Antidepressants	2,454 (6.7%)	2,079 (6.5%)	3,802 (7.0%)	3,171 (6.8%)
Asthma / COPD	3,828 (10.5%)	3,165 (10.0%)	5,865 (10.8%)	4,860 (10.4%)
Population ≥40	N=28,906	N=24,816	N=45,390	N=38,855
Heart disease	2,710 (9.4%)	2,063 (8.3%)	4,539 (10.0%)	3,583 (9.2%)

[1] See table 6.1 for ATC codes.

Table A6.2 Two by two-tables for self-reported vs. medication use base outcomes.

Medication		"Have you been treated or monitored for this by a general practitioner or a specialist in the past 12 months?'' (Kappa: 0.90)			"Do you have diabetes?" (Kappa: 0.91)		
Diabetes medication in the year of the survey		**yes**	**no**	**missing**	**yes**	**n**	**missing**
	yes	2,479	158	137	2,485	120	169
	no	362	32,664	817	342	32,256	1,245

		"Have you been treated or monitored for this by a general practitioner or specialist in the past 12 months?' (Kappa: 0.63)			"Did you have asthma or COPD in the last 12 months?'' (Kappa: 0.66)		
Asthma/COPD medication in the year of the survey		**yes**	**no**	**missing**	**yes**	**no**	missing
	yes	1,871	1,580	377	2,339	1,236	253
	no	361	30,239	2,189	804	29,845	2,140

		"Have you been treated or monitored for this by a general practitioner or specialist in the past 12 months?'' (Kappa: 0.66)			"Did you have hypertension in the last 12 months ?" (Kappa: 0.67)		
Hypertension medication in the year of the survey		**yes**	**no**	**missing**	**yes**	**no**	**missing**
	yes	6,484	3,800	1,303	7,247	3,467	873
	no	598	22,833	1,599	1,029	22,448	1,553

		Psychological distress (Kessler≥30) (Kappa: 0.20)		
Antidepressants in the year of the survey		**yes**	**no**	**missing**
	yes	491	1,881	82
	no	1,140	32,165	858

Table A6.3a Distribution of UFP from aviation, other air pollutants and noise in the PHM 2012 (n=36,617) (UFP in #/cm³; other air pollutants in µg/m³, noise in dB (Lden)).

	Mean	SD	p1	p5	p10	p25	p50	p75	p90	p95	p99
UFP	**1,745**	**1,151**	**625**	**744**	**901**	**1,151**	**1,424**	**1,872**	**2,807**	**3,976**	**7,342**
Other air pollutants											
PM25	14.1	0.8	12.7	13.1	13.3	13.6	13.9	14.4	15.0	15.8	16.2
NO_2	25.3	3.2	19.0	21.1	21.8	23.0	24.8	27.1	29.8	31.6	33.8
EC	1.0	0.2	0.7	0.8	0.8	0.8	0.9	1.1	1.2	1.3	1.5
PM2.5-EC	13.1	0.7	12.0	12.3	12.4	12.8	13.0	13.3	13.8	14.5	15.4
Noise											
Aviation (Schiphol)	46.5	3.5	41.2	41.8	42.5	44.1	45.9	48.2	52.5	53.0	57.2
Road	52.8	6.3	40.6	43.7	45.4	48.3	52.0	56.8	61.6	64.3	69.0
Rail	34.9	8.7	24.0	24.0	24.0	27.7	33.8	40.2	47.2	51.2	58.6

Table A6.3b Distribution of UFP from aviation, other air pollutants and noise in the PHM 2016 (n=54,263) (UFP in #/cm³; other air pollutants in µg/m³, noise in dB (Lden)).

	Mean	SD	p1	p5	p10	p25	p50	p75	p90	p95	p99
UFP	**2,204**	**1,423**	**797**	**891**	**1,019**	**1,384**	**1,744**	**2,633**	**3,905**	**5,083**	**7,953**
Other air pollutants											
PM25	11.2	0.7	9.8	10.3	10.5	10.7	11.1	11.5	12.0	12.7	13.8
NO_2	21.6	3.4	15.2	16.7	17.7	19.1	21.2	23.5	26.1	28.0	30.8
EC	0.9	0.1	0.6	0.7	0.7	0.8	0.9	0.9	1.0	1.1	1.3
PM2.5-EC	10.3	0.6	9.2	9.6	9.7	9.9	10.2	10.5	11.0	11.6	12.5
Noise											
Aviation (Schiphol)	47.2	3.8	40.6	41.6	42.8	45.0	46.6	49.0	52.5	54.3	58.1
Road	52.7	6.3	40.5	43.7	45.3	48.2	51.9	56.7	61.6	64.3	68.9
Rail	34.9	9.1	24.0	24.0	24.0	26.4	34.0	40.6	47.6	51.8	59.3

Table A6.4 Comparison of effect estimates derived from the combined dataset (including both 2012 and 2016) and pooled effect estimates from the 2 separate datasets.

	2012		2016		POOLED		Combined dataset	
outcome	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Primary outcomes								
SPH	1.06	(0.87, 1.29)	0.96	(0.83, 1.09)	0.99	(0.88, 1.11)	0.99	(0.89, 1.11)
Distress	1.06	(0.87, 1.28)	0.93	(0.81, 1.06)	0.97	(0.87, 1.08)	0.95	(0.85, 1.05)
Medication use								
Depression	1.01	(0.88, 1.17)	0.95	(0.86, 1.05)	0.97	(0.90, 1.06)	0.97	(0.89, 1.05)
Diabetes	1.12	(0.97, 1.28)	1.06	(0.97, 1.17)	**1.08**	**(1.00, 1.17)**	**1.08**	**(1.00, 1.17)**
Hyper-tension	**1.16**	**(1.06, 1.27)**	1.00	(0.94, 1.07)	**1.05**	**(1.00, 1.10)**	**1.05**	**(1.00, 1.10)**
Heart disease	1.08	(0.94, 1.23)	1.02	(0.93, 1.13)	1.04	(0.96, 1.13)	1.03	(0.96, 1.11)
Asthma	0.97	(0.86, 1.09)	1.04	(0.95, 1.13)	1.01	(0.95, 1.08)	1.02	(0.95, 1.09)

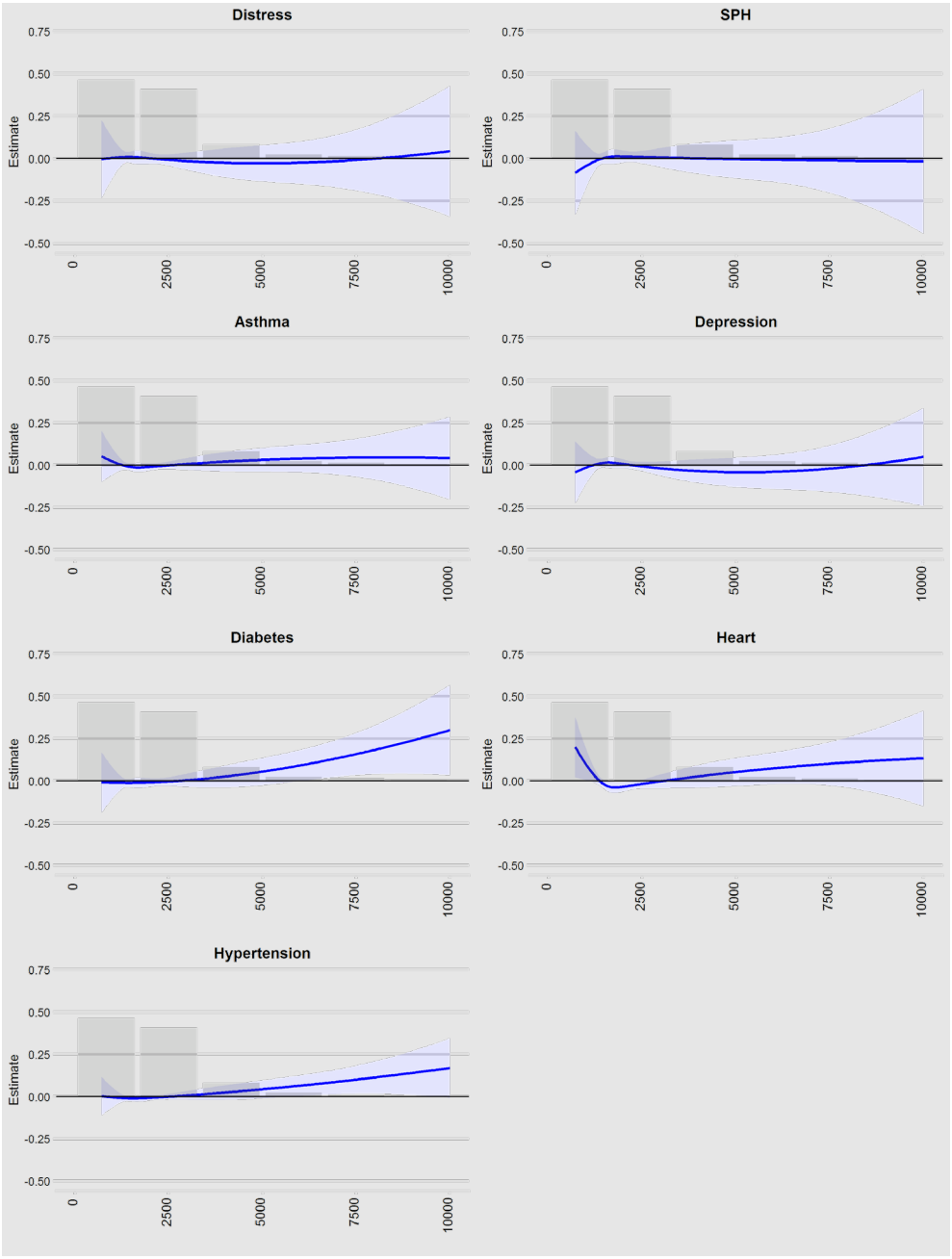


Figure A6.1a Natural cubic splines (3 df) for the association between UFP from aviation and outcomes available for both 2012 and 2016, after excluding the four municipalities with the lowest average UFP concentrations.

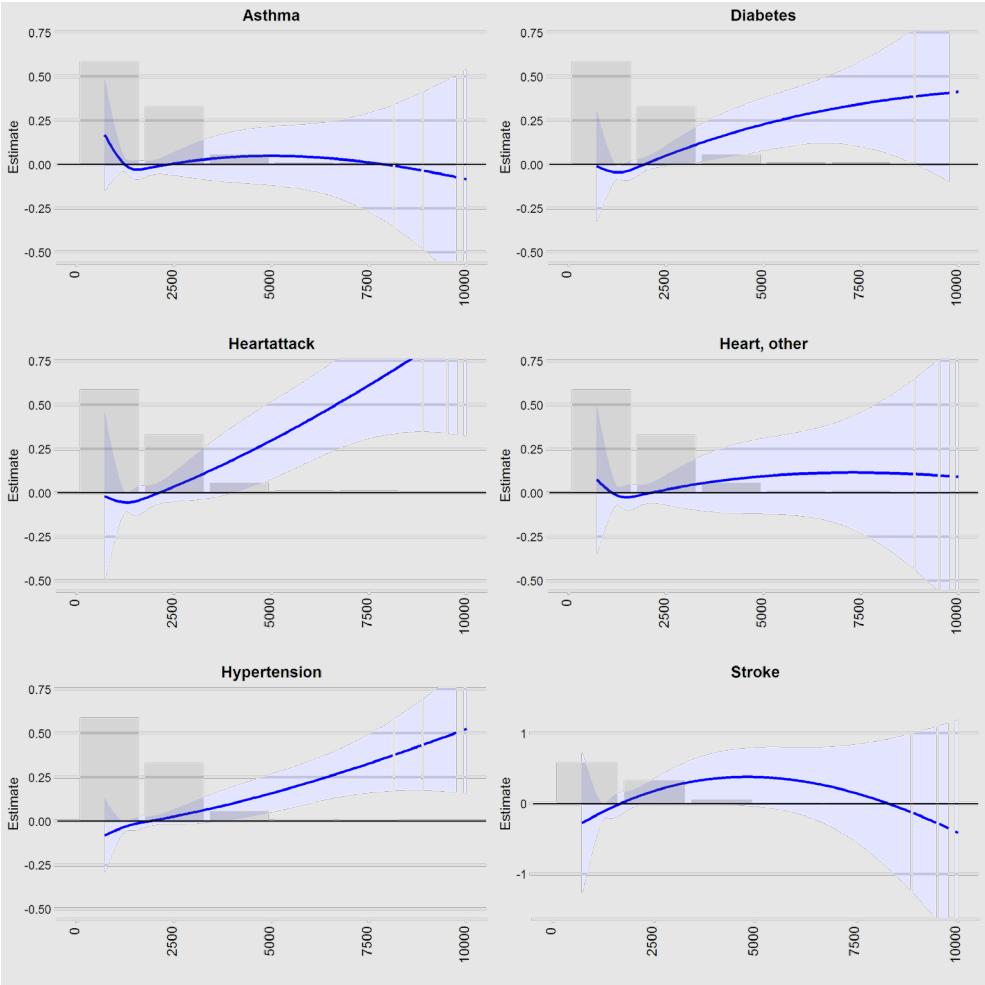


Figure A6.1b Natural cubic splines (3 df) for the association between UFP from aviation and self-reported physician treated disease (available for 2012 only), after excluding the 4 municipalities with the lowest average UFP concentration.

7 Discussion and conclusions

7.1 Introduction

In this chapter we present the overall discussion and integrated conclusion of the different studies on long-term effects, taking into account the earlier findings of the short-term studies and the available literature on aviation UFP and general UFP.

We conducted a large number of analyses for multiple outcomes, including both study-specific outcomes (e.g. pregnancy outcomes), as well as similar outcomes in different substudies (e.g. asthma or diabetes). In the main findings sections of the previous chapters we have evaluated the results for all individual outcomes separately, resulting in a classification of all outcomes as either *clear, probable, possible, weak, no* or *inverse* association (see 2.11). We use this classification as a starting point in the overall interpretation.

We *a priori* distinguished between primary and secondary outcomes, as described in paragraph 2.3.2. In the overall interpretation of the results, most weight is put on the results of the primary outcomes.

In this chapter we integrate the findings per type of effect (i.e. general, respiratory, cardiovascular, metabolic, mental health, nervous system and pregnancy outcomes). In the evaluation of the different effects, we consider the following components:

1) Results of the studies on effects of long-term exposure to UFP from aviation around Schiphol Airport (described in this report).
2) Results of the studies on effects of short-term exposure from UFP around Schiphol Airport (Janssen et al, 2019).
3) Results from studies around other airports (where available).
4) Results from studies on effects of UFP from all sources.

We primarily used the recent advice of the Dutch Health Council (Gezondheidsraad, 2021) on the health risks of ambient UFP, and looked for papers that were published after the completion of the Health Council report.

In our conclusions we follow the classification of the Health Council and the EPA in describing the evidence of relationship between UFP from aviation and health effects as: *"causal"*, *"likely"*, *"suggestive"*, *"inadequate"*, and *"no indications"* (see Appendix, table A7.1).

7.2 Main findings

Table 7.1 summarizes the classification of the associations for all individual outcomes, as described in paragraph 3.4 (mortality), 4.4 (pregnancy outcomes, 5.4 (medication use) and 6.4 (health monitor).

Table 7.1 Summary of classification of the associations, per type of effect and per sub study.

Health outcome	Mortality	Perinatal registration	Medication	Public Health Monitor
Mortality	**Natural mortality**	*Infant mortality*		
General health				**Self perceived health**
Respiratory	**Respiratory mortality**		**Asthma/COPD (20+)** **Asthma/COPD(6-19 yrs)** **Asthma/COPD(0-5 yrs)**	*Asthma/COPD (self-reported)* *Asthma/COPD (medication)*
	Lung cancer *COPD mortality*			
Cardiovascular	**Cardiovascular mortality** *Ischaemic heart disease* *Arrythmia* *Stroke* *Cerebrovascular disease*		**Heart disease**	*Heart disease (medication)* *Heart attack* *Stroke* *Other heart disorder*
			Hypertension	*Hypertension (self-reported)* *Hypertension (medication)*

No association: Probable association: Possible association: Clear association: Inverse association:

Primary endpoints in **bold**; secondary endpoints in *italic.*

Table 7.1 Summary of classification of the associations, per type of effect and per substudy (continued).

Health outcome	Mortality	Perinatal registration	Medication	Public Health Monitor
Metabolic				
	Diabetes		**Diabetes**	*Diabetes (self-reported)* *Diabetes (medication)*
Neurodegenerative				
	Neurodegenerative disease *Parkinson's disease* *Dementia* *Alzheimer's disease*		**Parkinson's disease** *Dementia*	
Psychological complaints				
			Antidepressants (20+)	**Psychological distress** *Antidepressants (medication)*
			Antidepressants (6-19 yrs) *ADHD (16-19 yrs)*	
Birth outcomes				
		Preterm birth **Low birth weight** **Small gestational age** *Congenital anomalies* *Apgar scores*		

No association: Probable association: Possible association: Clear association: Inverse association:

Primary endpoints in **bold**; secondary endpoints in *italic*.

7.2.1 General health: mortality and self-perceived health

Natural mortality, infant mortality

This study

We found no association between UFP from aviation and natural mortality. We also found no association with infant mortality in the pregnancy outcomes substudy.

Our observation of no association between exposure to UFP from aviation and natural mortality is in line with the results of an earlier ecological explorative study (Janssen et al., 2016), in which no evident indications of deviation in mortality risks between residential areas near Schiphol and rest of the Netherlands were observed.

Other UFP studies

To our knowledge there are no studies investigating natural mortality in relation to long-term UFP-aviation exposure around other airports. In a 2015 study in California, Ostro and colleagues (2015) found no association between long-term exposure to general UFP and all-cause mortality. There are no studies investigating acute effects of UFP from aviation on all-cause mortality.

Health Council classification

The Dutch Health Council classified the evidence for effects of exposure to UFP on all-cause mortality as "inadequate", given the limited literature available.

Self-perceived health

This study

We found no associations between UFP from aviation and self-perceived health. Self-perceived health is labelled as a primary outcome, as this information is not available in any of the other registries.

Other UFP studies and Health Council classification

Self-perceived health was not addressed in the Health Council report, and to our knowledge no other studies have considered this endpoint in relation to UFP from aviation or from other sources.

Conclusion

For the three indicators of general health (natural mortality, infant mortality and self-perceived health) we conclude that there are no indications of effects of long-term exposure to UFP from aviation around Schiphol Airport.

7.2.2 Respiratory

This study

We found no association with UFP from aviation for any of the respiratory outcomes evaluated in this study, either primary or secondary. This includes potential effects on adults (i.e. mortality, medication use and self-reported respiratory health) as well as children (medication use).

Short-term study
We have previously shown that *short-term* exposure to ultrafine particles, as occurs around Schiphol, is associated with acute health effects on the respiratory system. This conclusion was based on three different studies, including a panel study with schoolchildren (real-life concentrations), a volunteer study with healthy young adults (high concentrations) and a toxicological study in lung cells. In schoolchildren, we observed significant associations between exposure to UFP and an increase in daily respiratory symptoms and bronchodilator use, which is considered health relevant (Janssen et al, 2019).

Other UFP studies
To our knowledge, no other studies are available on the effects of long-term exposure to ultrafine particles from aviation around other airports. A study by Habre and colleagues (2018) near Los Angeles Airport found that short-term exposure to traffic-related UFP was associated with decreased lung function, while short-term exposure to airport-related UFP was associated with increased acute systemic inflammation.

Two large Canadian cohort studies documented an association between long-term exposure to general UFP on the incidence of asthma in children and COPD in adults respectively (Lavigne et al, 2019; Weichenthal et al, 2017). Some of the associations were sensitive to adjustment for other air pollutants. A cohort study in California, investigating effects of long-term exposure to PM0.1, found no association with respiratory mortality (Ostro et al, 2015). A cross-sectional study among schoolchildren in Brisbane found no association between long-term exposure to UFP and chronic respiratory disease, lung function or exhaled NO, while UFP was associated with increased C-reactive protein (CRP) in the blood, a marker for systemic inflammation (Clifford et al, 2018). A recent study - not yet included in the report of the Dutch Health Council - investigated the associations of long-term exposure to PM composition and UFP with lung function at the age of 16 in the Dutch PIAMA cohort, and found no evidence for an independent effect of UFP exposure (Yu et al, 2021).

Health Council classification
The Dutch Health Council classified the evidence for effects of exposure to UFP on respiratory health as "suggestive". This classification was mainly based on the two large Canadian cohort studies described above, as well as on evidence from experimental and short-term studies.

Difference between results of short-term and long-term studies
There are several explanations for the reason why UFP from aviation around Schiphol Airport is associated with short-term effects, but not with long-term effects. For other air pollutants, several studies have indicated that air pollution is associated with exacerbation of symptoms, rather than incidence (ref). In a review of 16 studies published until December 2018, Da Costa et al (2019) found associations between children's health (including mainly short-term studies on respiratory outcomes) and exposure to UFP, especially among children with respiratory diseases. Also, effects of short-term exposure may be easier to detect for methodological reasons (see 7.4.3).

Conclusion
We found no indications that long-term exposure to UFP from aviation around Schiphol airport causes respiratory disease, but short-term exposure may aggravate respiratory symptoms and medication use in residents that already have a respiratory disease.

7.2.3 Cardiovascular

This study
We did not find clear associations between residential exposure to UFP from aviation and any of the primary outcomes across the sub-studies. We did find a probable association with the use of heart disease medication. For secondary outcomes, we found clear associations for heart attack (self-reported) and hypertension prevalence (based on both medication use and self-reporting of doctor diagnosis), a probable association for arrythmia mortality and possible associations with self-reported stroke and medication use for heart disease in the PHM substudy. We observed no associations for total and other sub-classes of cardiovascular mortality, incidence of hypertension and self-reported other heart disorders. Together, this provides suggestive evidence of cardiovascular effects of UFP-aviation exposure around Schiphol Airport.

Short-term study
We previously conducted a study on the effects of short-term exposure to UFP near Schiphol. In this volunteer study we saw some biological responses that are in line with cardiovascular outcomes in the current study. Specifically, directly after a five-hour exposure to UFP from aviation we saw that the QTc interval prolonged by 9.9 ms (Janssen et al., 2019, Lammers et al., 2020). QTc describes the duration of ventricular repolarization, corrected for heart rate. It has previously been reported that extension of the QTc interval by >5 ms can increase the risk of cardiac arrhythmias in patients with heart disease (FDA, 2005). We also found that short-term exposure to UFP from aviation was significantly associated with reductions in, among others, urinary dimethylamine concentrations (Selley et al., 2021). The reduction in dimethylamine is an indicator of decreased nitric oxide synthesis. Nitric oxide has been reported to play a crucial role in protecting the heart against injury, regulating the ability of the heart muscle to contract, and cardiac remodelling after infarction (Rastaldo et al., 2007).

Other UFP studies
To our knowledge, there are no studies investigating the association between long-term exposure to UFP from aviation and cardiovascular health effects. A study by Habre and colleagues (2018) found increased acute systemic inflammation following short-term exposure to UFP from Los Angeles airport. Investigating general UFP, a study in California associated long-term exposure to UFP with ischemic heart disease mortality (Ostro et al., 2015). Two studies in Canada found an association with increased risk of hypertension, congestive heart failure, and acute myocardial infarction (Bai et al., 2018, Bai et al., 2019). A study in the Netherlands found an association with increased risk of cardiovascular disease, including myocardial infarction and heart failure (Downward et al., 2018).

Health Council classification
The Dutch Health Council classified the evidence for effects of exposure to UFP on cardiovascular health as "suggestive", based on the strength of both epidemiological and toxicological scientific evidence.

Conclusion
We conclude that there is suggestive evidence for effects of exposure to UFP from aviation around Schiphol airport on cardiovascular health, based on the joint results of this study, our volunteer study near Schiphol airport, as well as the literature on both short-term and long-term effects of UFP in general.

7.2.4 Metabolic

This study
In the primary outcomes we found no association between exposure to UFP from aviation and diabetes medication use in the medication substudy (diabetes incidence). In contrast, among secondary outcomes we found clear associations between exposure to UFP from aviation and diabetes in the PHM substudy. The association was present for both self-reported, physician treated diabetes and diabetes medication use (diabetes prevalence). In the substudy on mortality, we classified the association between UFP exposure and diabetes mortality as "no association". In our interpretation, we put most weight on the results of the primary outcomes ("inadequate" evidence), but we recognise that the clear associations in one of the secondary endpoints warrant further investigation.

Other UFP studies
To our knowledge there are no studies investigating the association between long-term exposure to UFP from aviation and diabetes mortality and/or morbidity in the vicinity of other airports. There were three studies investigating long-term general UFP exposure and metabolic health outcomes. A study in Canada associated an increase in UFP with increased diabetes incidence (Bai et al., 2018), a study in Germany linked increased UFP to elevated levels of an insulin resistance marker (Zhang et al., 2021), and a cross-sectional study in Spain found an association with overweight and obesity in schoolchildren (de Bont et al., 2019). There is no scientific evidence relating short-term exposure to (general) UFP and metabolic disorders.

Health Council classification
Based on the limited literature available so far and the lack of experimental studies, the Dutch Health Council classified the evidence for an association between UFP exposure and metabolic effects as "inadequate".

Conclusion
We conclude that at this point there is inadequate evidence for effects of exposure to UFP from aviation around Schiphol airport on metabolic disease, based on the results of the current study and limited literature. However, given the clear associations in the Public Health Monitor substudy, further investigation is warranted.

7.2.5 *Nervous system*

For effects on the nervous system, we will discuss the results and literature separately for outcomes related to neurodegenerative disease and psychological complaints.

This study

Neurodegenerative disease

To our knowledge, ours is the first study to look into the association between long-term exposure to UFP from aviation and mortality from or incidence of neurodegenerative disease.

Both primary outcomes -mortality due to neurodegenerative diseases and incidence of medication use for Parkinson's disease - did not show positive associations with UFP from aviation. For the incidence of medication for Parkinson's disease no association was observed, and for mortality due to neurodegenerative diseases the association was not in the expected direction (see Table 7.2).

The results of the incidence and mortality studies on dementia are inconsistent. Medication use for dementia was clearly associated with UFP. Mortality due to dementia had an association with UFP in the opposite direction. If the incidence is related to UFP exposure, this is expected to be reflected in the subsequent mortality as well. This is clearly not the case. So what remains is an isolated indication of a risk for the incidence of medication use for dementia syndromes. For the other secondary endpoints, we found a possible association with mortality due to Alzheimer's disease and an inverse association with mortality due to Parkinson's disease.

Psychological complaints

None of the outcomes related to psychological complaints showed an association with UFP from aviation in the expected direction. Psychological distress and the prevalence of antidepressants, both assessed in the population taking part in the Public Health Monitor, were classified as "no association". The same classification was given to the incidence of antidepressants among the population of 20 years and older. The incidences of ADHD medication and of antidepressants in the younger age groups were classified as "inverse associations", which is considered biologically implausible.

Other UFP studies

Neurodegenerative disease

We did not find reports of studies that examined the association with long-term exposure to UFP from other sources. This is also the case for studies on short-term exposure to UFP. It is therefore not possible to compare our findings with results from other studies.

Psychological complaints

Two studies were carried out into the short-term effects of UFP on psychological complaints. Wang et al. (2014) did not find evidence for an association with depressive symptoms in older adults. Mehta et al. (2016) studied the association of several air pollutant components with perceived stress in older men. The strongest associations were observed for UFP. In both studies the results were not adjusted for co-pollutants.

The results of our studies cannot be compared with the results of abovementioned studies, since we addressed the long-term exposure to UFP.

Cognition
There is one epidemiological study that looked into the effects of UFP on cognition. Sunyer et al. (2015) studied the association between UFP and cognitive growth in schoolchildren. We did not look into the effects on cognition (see 2.3.2).

Health Council classification
The Health Council summarised that there is evidence from animal studies that UFP deposited in the nasal cavity can reach the brain directly through absorption by the nasal mucosa and olfactory nerves, and that in a study with volunteers brain activity was shown to be modified by peak exposure to UFP. The strength of evidence for neurological effects was classified as "suggestive", largely based on the biological plausibility and on the results of experimental studies.

Conclusion
We included health outcomes related to the nervous system in the programme, given the earlier evidence for a mechanism that UFP can reach the brain. For neurodegenerative disease and for psychological complaints, we conclude that there is inadequate evidence for effects of exposure to UFP from aviation around Schiphol Airport. We observed an isolated indication of a risk for the incidence of medication use for dementia syndromes. It is recommended to include this endpoint in epidemiological studies into the health effects of UFP.

7.2.6 Pregnancy outcomes

This study
We found a possible association between exposure to UFP from aviation and preterm birth and SGA, which were defined as primary health outcomes. For these outcomes, effect estimates in the main model were positive but not statistically significant. Some associations reached statistical significance in the sensitivity analyses. In addition, associations between UFP from aviation and gestational age as continuous outcome were statistically significant. We found no association between UFP from aviation and low birth weight.

For secondary outcomes, we found a probable association between exposure to UFP from aviation and congenital anomalies. Although associations in the main model were not significant, all studied congenital anomalies showed a positive trend in the main model and most splines, and reached statistical significance in some of the sensitivity analyses. We found no associations between UFP from aviation and the other secondary health outcomes (infant mortality before age 1 and Apgar-score).

Other UFP studies
Wing and colleagues were the only group that studied the relationship between exposure to UFP from aviation and preterm birth. Preterm birth occurred in 8.7% of all births from 2008 to 2016 among mothers living within 15 km of Los Angeles International Airport (LAX). The OR per IQR

increase (9,200 pts/cm^3) in UFP exposure was 1.04 (95% CI:1.02,1.06), after adjusting for maternal demographic characteristics, exposure to traffic-related air pollution and airport-related noise (Wing et al., 2020). However, UFP-levels from aviation around LAX were considerable and significantly higher than in the Schiphol area, and effect estimates expressed per 3,500#/cm^3 increase around LAX (OR: 1.015) were of the same order of magnitude as found in the area around Schiphol [Schiphol OR=1.03 ((0.97-1.09) adjusted for NO_2]. None of the other pregnancy outcomes were included in the study by Wing et al.

Four other epidemiological studies were published on the effect of general or road UFP on pregnancy outcomes. A study in Toronto examined the association between prenatal exposure to ambient UFPs and congenital heart defects (CHDs), and found a significantly increased association between UFP exposure and ventricular septal defects, but not with CHDs overall (Lavigne, 2019). We were only able to study the effects of UFP on overall circulatory congenital anomalies. Studies in California found associations between UFP and an increased risk of low birth weight and preterm birth. All associations were not adjusted for co-pollutants (Laurent et al., 2014, Laurent et al., 2016a, Laurent et al., 2016b).

A systematic review that summarized 74 toxicological studies on placental translocation of particles, shows that ultrafine particles can bypass the placenta barrier and enter the amniotic fluid and the circulation and various organs of the developing foetus (Bongaerts et al., 2020). This may explain the biological mechanisms that cause the adverse health outcomes.

Health Council classification
The Dutch Health Council concluded that although there are still uncertainties about the possible risks and some limitations of the epidemiological studies performed so far, the overall evidence for a relationship between UFP exposure and adverse growth and development effects of the foetus is "suggestive".

Conclusion
We conclude that there is suggestive evidence for effects of exposure to UFP from aviation during pregnancy and pregnancy outcomes. This is based on the results of this study and on results of other studies on UFP in relation to pregnancy outcomes, including a study near another airport. This warrants further investigation into the effect of exposure to UFP from aviation on pregnancy outcomes.

7.3 Potential impact

In the previous chapters we expressed the potential adverse health effect of UFP from aviation as an additional risk, indicated as Hazard Rate (HR) or Odds Ratio (OR) per 3,500 #/cm^3. The size of the HR and the OR reflects the risk for people with a high exposure to UFP from aviation (5% highest), compared to people with a low (5% lowest) exposure. The 3,500 #/cm^3 is thus (approximately) the variation that occurs in the study area, in terms of exposure to UFP from aviation.

To provide insight in the additional potential risk of UFP from aviation for health, we first selected the main type of health outcome for which the adverse health effect due to UFP was classified as at least 'suggestive' in paragraph 7.2. These are cardiovascular health and pregnancy outcomes. Subsequently within these groups we chose the primary and secondary health endpoints that were classified as having at least a 'probable' association with UFP from aviation, and that were assessed for the whole population with the use health registries (see Table 7.1): incidence of medication use for heart disease (among 40 years and older), mortality due to arrythmia (among 30 years and older) and (any) congenital anomalies. We used the HR's and OR's of the main model (see Table 7.2, second column) to express the additional risk.

The incidence of medication for heart disease was about 3% higher in relative terms, when comparing people with high and low exposure to UFP from aviation. For mortality from arrhythmia it was 8%, and for (any) congenital anomalies 5%. Over the duration of the study (12 years), for every 10,000 residents with a low exposure 1,400 started taking medication for heart disease. Among the residents with a high exposure, it is estimated that an additional 40 out of 10,000 people started taking medication for heart disease (3% of 1,400 people).

In 12 years, 40 people per 10,000 residents with a low exposure died from cardiac arrhythmia. For high exposure we estimated an additional 3 cases per 10,000 residents (8% of 40). For (any) congenital malformations, the estimated annual increase is 8 per 10,000 births (5% of 154 per 10,000 births).

In an exploratory study into the health risks of UFP from aviation around Schiphol airport, we estimated the number of deaths that could be attributed to the exposure to UFP from aviation (Janssen et al., 2016). At that time only a result of an expert elicitation study was available, in which eleven European experts from various disciplines (clinical medicine toxicology and epidemiology) estimated an exposure-response relationship for generic UFP and all-cause mortality (Hoek et al., 2010). Since additional risks expressed per 3,500 #/cm^3 do not give an insight into how many residents may have been affected by UFP from aviation, we updated the estimated number of cases per year that can be attributed to the exposure to UFP from aviation, under the assumption that the relation between exposure and health effect is causal.

We calculated the 5-year mean concentration between 2015-2019 at residential addresses in the study area. We used the 1 percentile of the population weighted UFP concentration in the study area (760 #/cm^3) as the exposure level from which the additional risk started. The population was estimated at 2,24 million inhabitants on January 1, 2019. The mean population weighted UFP concentration was 2,100 #/cm^3, and the 99 percentile was 6,800 #/cm^3. We calculated the population attributable fraction (PAF), based on the exposure distribution and on the HR (or OR) and the population per exposure level. The PAF is the proportional reduction of a disease or mortality in a population (in this case the study area) that would occur if the exposure to a risk factor were reduced to an alternative ideal exposure scenario (in this case 760 #/cm^3). We

subsequently calculated the potential additional cases per year, based on the incidence per year of the health outcome (see Table 7.2).

Table 7.2 Potential size of the burden of disease in the study area in the period 2015-2019 for cardiovascular health outcomes and pregnancy outcomes with a probable association with UFP from aviation, under the assumption of causality.

Health outcome	HR or OR per 3,500 #/cm3 (95% CI)	Population Attributable Fraction (%)	Incidence per year	Attributable cases per year
Mortality due to arrythmia (among 30 years and older)	1.084 (0.980, 1.198)	3.04 (0-6.68)	444	14 (0-30)
Incidence of medication use for heart disease (among 40 years and older)	1.025 (0.997, 1.054)	0.94 (0-2.0)	12,800	120 (0-255)
Congenital anomalies (any)	1.054 (0.980, 1.134)	2.0 (0-4.7)	339	7 (0-16)

It is estimated that exposure to UFP from aviation could lead to 14 deaths due to arrythmia, 120 incident cases of medication use for heart disease and 7 births with congenital anomalies per year in the study area, if the relations with UFP from aviation are causal.

It should be noted that the classification of the strength of the evidence for effects on cardiovascular health and pregnancy outcomes is "suggestive", and that for all three endpoints, the associations with UFP were classified as "probable", but not as "clear". Therefore, the provided additional risks and the results in Table 7.2 about the burden of disease should be interpreted as an illustration of the potential impact of UFP from aviation, that may occur if there is causality.

For the three outcomes in table 7.2 the effect estimate in the main model was close to statistical significance, and generally stable across the different sensitivity analyses. For pregnancy outcomes, in addition to the probable association for congenital anomalies, the associations with preterm birth and SGA were classified as "possible''. For these outcomes, effect estimates of the main model were less precise, and the classification was mainly based on the overall pattern, including more elevated effect estimates in some of the sensitivity analyses. For example, for preterm birth the estimated number of attributable cases would be 8 (0-32) based on the main model, 23 (1-46) based on the analyses without the 4 municipalities with the lowest UFP concentrations and 37 (13-60) after non-linear adjustment for NO_2. The variability in the results also illustrates why we made a distinction between "probable" and "possible" in the classification of health endpoints.

In the health impact assessment of the explorative study a relative risk (RR) of 1.003 per 1,000 #/cm^3 and a (smaller) study area of 1.2 million inhabitants aged 30 years or older were used. This RR was not specific

for emissions from aviation, but for UFP from all sources. The PAF was 0.78%, which corresponded with about 120 premature deaths per year with a 95% confidence interval of 40 to 370. Based on the results in Table 7.2 it can be concluded that the estimated potential impact of UFP from aviation on mortality is lower than the estimate reported in the explorative study. The main explanation for the lower estimate is that the substudy on mortality did not reveal a relation with all-cause mortality, but only found an association with mortality due to arrythmia. Since deaths due to arrythmia are a fraction of the total mortality (about 2.9%), the estimated number of cases is much lower, although the HR for arrythmia (1.084 per 3,500 #/cm^3) is higher than the earlier applied HR for all-cause mortality (1.003 per 1,000 #/cm^3 ~ 1.011 per 3,500 #/cm^3). Additionally, the exposure assessment of UFP from aviation has improved since the publication of the explorative study.

7.4 Methodological aspects

7.4.1 Classification of exposure to UFP from aviation

We used a dispersion model to estimate residential outdoor concentrations of UFP from aviation for all addresses in the study area. Estimated outdoor concentrations at the residential address are generally used to characterize long-term exposure to air pollution in epidemiological studies. A detailed comparison was carried out between modelled and measured concentrations, based on six-months measurement periods in ten locations at different distances and orientations from the airport and it was concluded that the model was suitable for application in our epidemiological studies (Voogt et al, 2019).

We used actual hourly flight and meteorological data to estimate the monthly averaged UFP from aviation for all months in the period 2003-2019, for all addresses in the study area. This allowed us to calculate average concentrations for varying exposure windows, depending on the requirements of the specific study, and also to incorporate residential history. For the studies on mortality, medication use and the Public Health Monitor, we evaluated associations with one to five-year average exposures; for pregnancy outcomes we evaluated exposure during pregnancy as well per trimester for all outcomes except congenital anomalies. For the latter, we focused on the second month of pregnancy (see below). One to five-year averages were generally highly correlated ($R \geq 0.9$). Correlations between different trimesters of pregnancy were somewhat lower, with the lowest correlation between the first and third trimester ($R=0.6$). Effect estimates were generally similar for the different exposure windows in all studies, with exception of congenital anomalies, for which UFP-exposure during the second month showed the strongest association. This period is also considered as the most relevant time window for causation of congenital anomalies.

To get an indication of the effects of peak exposures (instead of long-term average exposures), we used the number of hours per month above 66,667 #/cm^3 (originally 100,000#/cm^3; see 2.5.4) as an alternative exposure metric. These indicators of peak exposure were generally highly correlated with the indicators of average exposure ($R>0.8$), and effect estimates were similar.

7.4.2 Confounding

7.4.2.1 Other air pollutants and noise

An important aspect in the interpretation of studies on the health effects of UFP in general is the generally high correlation with other air pollutants and/or noise, which makes it difficult to disentangle their independent effects. In our study UFP from aviation was poorly correlated with other air pollutants (PM2.5, NO_2, EC) and noise from road traffic, rail traffic or Schiphol. The highest correlation was observed with noise from Schiphol (R 0.3-0.5 for the different sub-studies). In our multi-pollutant models, associations were generally insensitive to adjustment for other air pollutants and noise, providing evidence for independent effects of UFP, where positive associations (i.e. clear, probable or possible) were observed.

7.4.2.2 Other sources of UFP

We specifically studied UFP from aviation. In addition to aviation, there are other sources of UFP such as road traffic and industry. At present there is no model available to estimate concentrations of UFP from all sources for all years in the study period, so we could not take the contribution of other sources into account in our analyses. UFP from road traffic is generally highly correlated with other traffic-related pollutants, such as EC and NO_2. By adjusting for these pollutants (see 7.4.2.1) we therefore indirectly also accounted for (part of) the contribution of UFP from road traffic. However, this analysis does not provide any information on the potential health effects of UFP from road traffic.

Exploratory measurements showed elevated UFP concentrations in the IJmond region, an area around a major industrial source (Weijers and Vonk, 2020). Excluding the three surrounding municipalities, as part of our sensitivity analyses, did not change the results for UFP from aviation.

7.4.2.3 Residual confounding

We adjusted for an extensive set of individual- and area-level SES indicators. However, our analyses may still be suffering from residual confounding, due to factors for which no information was available on an individual level, such as lifestyle factors. We used information on smoking, alcohol use, BMI and physical activity available in the PHM to evaluate potential residual confounding due to incomplete adjustment for these factors in the other sub-studies. Within the PHM, effect estimates for models including lifestyle factors were very similar to effect estimates from models only including covariates from administrative databases, suggesting very little confounding by these factors in this study. Indirect adjustment of associations with natural mortality for smoking status and BMI confirmed this finding.
For further interpretation of potential bias, we used the PHM to provide insight in potential differences in UFP exposure for, among others, current smokers compared to never smokers and obese people compared to normal weight people in different subsamples of the PHM. Unfavourable lifestyle factors were generally associated with lower exposure to UFP from aviation. This suggests that not adjusting for these factors could have resulted in an underestimation of the effect, especially for pregnancy outcomes for which we observed the largest

differences. However, this should be interpreted with caution, as differences were largely non-significant, possibly related to the small sample size.

For some outcomes (*e.g.*, preterm birth, mortality from neurodegenerative disease and most outcomes in the PHM), we observed a decreasing trend at the lowest concentrations. For most of these outcomes, this pattern was reduced when the four municipalities with the lowest UFP exposure were excluded. Exclusion of these four municipalities generally had no substantial effect on the effect estimates, with the exception of preterm birth and congenital anomalies, which became statistically significant. A possible but untested explanation is that differences between health practitioners or the distance to a health care facility can affect spatial differences in the baseline risk, and therefore may have influenced the trend at lower concentrations. It is not unlikely that there is a trade-off between the size of the study area, which defines the contrast in exposure and the power of the study, and the unexplained spatial heterogeneity in health outcomes that is introduced when the study area becomes too large. We have addressed spatial heterogeneity in our analyses, by including random effect models for district or municipality, where applicable. However, we cannot exclude that some regional heterogeneity remained, as exemplified by the patterns for dementia and Alzheimer mortality (see 3.1.2).

7.4.3 Study designs

In our research program we conducted different types of studies on the health effects of exposure to UFP from aviation. We used different designs, including a panel study and a volunteer study on effects of short-term exposure, cross-sectional studies on pregnancy outcomes and self-reported health, and longitudinal cohort studies on mortality and incidence of medication use. These varying designs have different advantages and disadvantages.

In our studies on short-term effects adjustment for personal characteristics is less relevant, as participants serve as their own controls. Also temporal variability in UFP (and other air pollutants), on which these studies rely, is substantially higher than the spatial variation that is used in the other designs. This was particularly the case in our panel and volunteer studies, as these were conducted relatively close to airport, with large temporal variation in UFP from aviation, related to meteorological conditions (*e.g.*, wind direction). As a result, acute effects of short-term (and to a lesser extent also mid-term) exposure could be easier to detect.

The study on pregnancy outcomes, although included in this report on effects of long-term exposure, represents more of a mid-term study, as the relevant exposure window is well-defined and restricted to a limited period of time. Also, (individual) confounders are assessed for the same time period.

Long-term studies provide information on morbidity and mortality, which contribute much more to the burden of disease than acute health effects of a temporary nature. However, these studies are more complicated in

terms of confounder adjustment, exposure and health outcomes characterization, as well as other spatial aspects. Finally, also given the considerations described in 7.4.2, we investigated the risk of an added long term UFP exposure from a single source in an already complex environmental situation, which may be difficult to detect.

7.4.4 Strengths and limitations

An important strength of our study is that we researched several different (types of) health effects in different complementary designs, which are likely prone to different types of bias. For example, the studies on mortality, pregnancy outcomes and medication incidence include all inhabitants in the entire study area, and can therefore be considered as unbiased representations of the total population. However, these studies lack information on lifestyle factors. This information is available in the PHM, which on the other hand is only based on a relatively small sample of the population. The study on medication incidence is a longitudinal study, which is considered a stronger design than the cross-sectional analyses on medication prevalence conducted within the PHM. However, in addition to lifestyle factors, the PHM also included information on self-reported disease. This can provide additional support, as registry-based prescribed medication, although more objective, only covers the disease that is medicated. The combination of different databases and designs allowed us to evaluate the consistency of the findings not only within a specific study, but also across the different studies. Additionally, in our evaluation of the findings, we were able to consider results from studies on effects of short-term exposure to UFP around Schiphol that were conducted as part of the same research program.

In addition to the large population size, other overall strengths of the study include the long study period (twelve years for mortality and medication use incidence, thirteen years for pregnancy outcomes) and the availability of the full residential history. The latter allowed us to apply selection criteria for time lived in the study area, and to consider moving into, out of or within the study area in the exposure assignment as well as in sensitivity analyses. We conducted a comprehensive set of (sensitivity) analyses to assess the robustness of the findings. Our extensive modelling, resulting in monthly averaged estimates of UFP from aviation for all months in the period 2003-2019 and all addresses in the study area, allowed us to evaluate different exposure windows. By conducting a comprehensive adjustment for other air pollutants and noise (see 7.4.2.1), we were also able to study the independent effects of UFP.

Compared with the only other study into the health effects of UFP from aviation, conducted around LAX airport, the long-term levels of exposure to UFP from aviation around Schiphol Airport are relatively low. The smaller contrast in long-term exposure levels may have affected the ability to detect possible associations between UFP from aviation and adverse health effects.

In three of the four substudies we lacked information on individual lifestyle factors. We adjusted for an extensive set of individual- and

area-level SES indicators, that could partly capture differences in lifestyle as well. Furthermore, we used individual level information on smoking, alcohol use, BMI and physical activity available in the PHM, to evaluate potential residual confounding due to incomplete adjustment for these factors in the other sub-studies. Within the PHM we found no indication of confounding by lifestyle factors (see 6.3.6.3). Bias could occur if for example smoking is more prevalent among residents with higher exposure to UFP from aviation. Analyses of the relation between exposure to UFP from aviation and lifestyle factors in different subsamples of the PHM showed that unfavourable lifestyle factors were generally associated with lower exposure to UFP from aviation. If bias due to incomplete adjustment for lifestyle factors has occurred, it is therefore more likely that this has resulted in an underestimation of the effect rather than an overestimation.

7.5 Conclusions

For a number of health outcomes there is suggestive evidence of adverse effects due to long-term exposure to UFP from aviation around Schiphol. This warrants further investigation, preferable in studies around multiple large (international) airports. More specifically:

- For cardiovascular disease, we conclude that there is suggestive evidence for effects of exposure to UFP from aviation around Schiphol airport, based on the joint results of this study, our volunteer study near Schiphol airport, as well as the literature on both short-term and long-term effects of UFP in general.
- For pregnancy outcomes, we conclude that there is suggestive evidence for effects of exposure to UFP from aviation during pregnancy. This is based on the results of this study and on results of other studies on UFP in relation to pregnancy outcomes, including a study near another airport.
- For respiratory disease, we conclude that there are no indications that long-term exposure to UFP from aviation around Schiphol airport causes this type of disease, but short-term exposure may aggravate respiratory symptoms and increase medication use in residents that already have the disease.
- For metabolic disease, we conclude that there is inadequate evidence for effects of long-term exposure to UFP from aviation around Schiphol airport, based on the results of the current study and limited literature.
- For neurodegenerative disease and psychological complaints, we conclude that there is inadequate evidence for effects of long-term exposure to UFP from aviation around Schiphol Airport.
- For the three indicators of general health (natural mortality, infant mortality, and self-perceived health), we conclude that there are no indications of effects of long-term exposure to UFP from aviation around Schiphol Airport.

Associations were generally insensitive to adjustment for other air pollutants and noise, providing evidence for independent effects of UFP.

The results of our comprehensive study on UFP from aviation increase the understanding of the potential health effects of long-term exposure to UFP, particularly from air traffic. In addition, the findings provide

further support for the conclusions of the Dutch Health council regarding suggestive evidence for effects of long-term exposure to UFP on cardiovascular health and on the growth and development of the foetus.

7.6 Recommendations for further research

All substudies were carried out around one airport. Given that there is suggestive evidence for several health outcomes, it is recommended to further investigate the risk of UFP from aviation, preferably around (international) airports with relatively large populations of residents exposed to both low and relative high exposure levels. The power of such a study can be substantially increased when it is carried out around multiple airports, following similar study designs.

Besides cardiovascular health and pregnancy outcomes, these studies should also include diabetes and dementia. Although we found inadequate evidence for effects of UFP from aviation on metabolic and neurodegenerative disease, the clear associations with diabetes in the public health monitor and with the incidence of medication use for dementia warrant further investigation.

7.7 Appendix

To assess the weight of the evidence for a causal relationship between exposure to UFP and adverse health effects, the Dutch Health Council distinguishes - in accordance with the EPA - between effects that are causal, probable, suggestive, insufficient or unlikely.

Table A7.1 Assessment of the weight of evidence by the Dutch Health Council (GR, 2021).

Classification	Description
Causal (in Dutch: *"aangetoond"*)	The relationship is demonstrated at relevant levels of exposure by consistent findings from multiple high-quality studies conducted by different research groups in different regions or countries. This applies, for example, if consistent effects are found in controlled, human exposure studies, or in observational studies in which the influence of chance, confounding or bias can reasonably be excluded, and where biological plausibility is supported by, for example, experiments.
Likely (*"waarschijnlijk"*)	The relationship is shown at relevant levels of exposure by multiple high-quality studies, where the results cannot be explained by chance, confounding or bias, but in which uncertainties remain. For example, when observational studies show links with health indicators which can also be attributed to exposure to other agents, or are insufficiently supported by, for example, animal experiments, or when toxicological animal experiments are not supported by human data.
Suggestive (*"indicatief"*)	There is evidence of a causal relationship at relevant levels of exposure, but there is still too much uncertainty to conclude that there is a (likely) causal relationship. For example, if the number of available studies is limited and the influence of chance, confounding or bias cannot be sufficiently excluded. This applies, for example, if there is only one high-quality epidemiological and/or toxicological study available that shows an association. If more studies indicating a health effect are available, this applies, for example, if the results are not completely consistent, but toxicological animal experiments do support biological plausibility.
Inadequate (*"onvoldoende"*)	The available studies are of insufficient quality, the results are not consistent, or there is insufficient statistical reliability to establish whether or not there is an association.
Not likely (*"onwaarschijnlijk"*)	A causal relationship is unlikely if multiple high-quality studies conducted at many different concentrations to which humans may be exposed show no adverse effect of increased exposure, even in people who may be particularly vulnerable.

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