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

Acute effects of particulate matter, nitrogen dioxide and ozone **in the Netherlands**

Evaluation of risks and impacts of air pollution and identification of vulnerable groups

RIVM letter report 2025-0132
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Colophon

DOI 10.21945/RIVM-2025-0132

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This research was carried out on behalf of the Ministry of Infrastructure and Water Management, Sustainable Environment and Circular Economy Directorate, as part of the assignments DLO.22 Air pollution and Health and DLO.23 support Clean Air Agreement (SLA) of Program 24 DLO Sustainable Living Environment.

Published by:
National Institute for Public Health and the Environment, RIVM
PO Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Synopsis

Acute effects of particulate matter, nitrogen dioxide and ozone in the Netherlands

Evaluation of risks and impacts of air pollution and identification of vulnerable groups

RIVM has investigated whether the risk of death following days with high air pollution levels changed between 1995 and 2019. To this end, the number of deaths following days with high concentrations of particulate matter, nitrogen dioxide or ozone in the air are compared with the numbers of deaths following days with lower concentrations. Some people are more sensitive to the harmful effects of air pollution and are more likely to die following days with higher concentrations.

The objective of the study is to assess whether the policy to improve air quality has led to fewer deaths following days with high air pollution levels. The policy aims to reduce the emission of air pollutants from sources such as traffic, agriculture and industry. This policy appears to have been effective. Between 1995 and 2019, fewer people died following days with high air pollution levels. This is because the concentrations of particulate matter and nitrogen dioxide decreased in this period.

RIVM also investigated *for each pollutant separately* what the risks are of dying following days with higher concentrations and whether these risks have changed over the years. There are no indications that the risk of dying after exposure to the same amount of particulate matter or ozone has changed. For nitrogen dioxide, this risk appears to have decreased. The reason for this remains unclear. It is still important for public health to reduce the *quantity* of air pollutants.

One point for attention is the concentration of ozone, which has remained the same or risen slightly in the years studied. As a result, ozone has become a more significant contributor, compared to the other two pollutants, in the number of deaths following days with higher concentrations. This calls for more knowledge on the acute health effects, such as mortality, of high exposure to ozone. And how exposure to ozone can be reduced.

It is also important to study which groups of people are more sensitive to the harmful effects of air pollution. This would allow for better warnings in the case of poor air quality. Generally, this concerns the elderly, young children and people with chronic conditions, but others may also be affected. An exploratory study showed that these groups are relatively easy to identify, but that a more accurate calculation method is needed. RIVM will work on developing this.

Keywords: air pollution, short-term exposure, acute effects, daily mortality, nitrogen dioxide, particulate matter, ozone, trends in risks, average-risk-approach, high risk groups

Publiekssamenvatting

Acute gezondheidseffecten luchtverontreiniging in Nederland

Evaluatie van risico's fijnstof, stikstofdioxide en ozon

Het RIVM onderzocht of tussen 1995 en 2019 de kans is veranderd om te overlijden na dagen met veel luchtvervuiling.
Hiervoor is vergeleken hoeveel mensen sterven na dagen met hoge concentraties fijnstof, stikstofdioxide of ozon in de lucht, en na dagen met lagere concentraties. Sommige mensen zijn gevoeliger voor de schadelijke effecten van luchtvervuiling en hebben na dagen met hogere concentraties een grotere kans om te overlijden.

Het doel van het onderzoek is te beoordelen of het beleid om de luchtkwaliteit te verbeteren, tot minder sterfgevallen leidt na dagen met hoge luchtvervuiling. Het beleid is erop gericht de uitstoot aan luchtvervuilende stoffen van onder andere verkeer, landbouw en industrie te verminderen. Dit beleid blijkt te hebben gewerkt. Tussen 1995 en 2019 zijn er minder mensen overleden na dagen met veel luchtvervuiling. Dat komt doordat de concentraties fijnstof en stikstofdioxiden in deze periode zijn gedaald.

Het RIVM onderzocht ook wat *per stof* de kans is om te sterven na dagen waarop de concentratie ervan hoger is. En of die kans door de jaren heen is veranderd. Er zijn geen aanwijzingen dat de kans om te overlijden na eenzelfde hoeveelheid fijnstof of ozon is veranderd. Deze kans lijkt voor stikstofdioxide kleiner te zijn geworden. Het is niet duidelijk waardoor dit komt. Voor de gezondheid blijft het belangrijk *de hoeveelheid* luchtvervuilende stoffen te verminderen.

Een aandachtspunt is de concentratie ozon, omdat deze in de onderzochte jaren hetzelfde is gebleven of iets is gestegen. Daardoor is ozon in verhouding tot de andere twee stoffen belangrijker geworden voor het aantal mensen dat sterft na dagen met hogere concentraties. Dat vraagt om meer kennis over de acute gezondheidseffecten, zoals sterfte, van een hoge blootstelling aan ozon. En hoe de blootstelling aan ozon kan worden verminderd.

Verder is het belangrijk te onderzoeken welke mensen gevoeliger zijn voor de schadelijke effecten van luchtvervuiling. Zij kunnen dan beter worden gewaarschuwd bij een slechtere luchtkwaliteit. In het algemeen zijn dat ouderen, jonge kinderen en mensen met een chronische aandoening, maar het kunnen ook anderen zijn. Uit een verkenning blijkt dat deze groepen vrij eenvoudig in beeld te brengen zijn, maar daar wel een betere rekenmethode voor nodig is. Het RIVM gaat daaraan werken.

Kernwoorden: luchtverontreiniging, kortdurende blootstelling, acute effecten, dagelijkse sterfte, stikstofdioxiden, fijnstof, ozon, verandering in risico's, gemiddelde-risico-benadering, hoogrisico groepen

Contents

Beleidssamenvatting

Blootstelling aan luchtverontreinigende stoffen, zoals fijnstof (PM), stikstofdioxide (NO_2) en ozon (O_3), wordt in verband gebracht met een breed scala aan gezondheidseffecten. Deze effecten zijn aangetoond in zowel korte-termijnstudies, die verandering in blootstelling van enkele uren tot dagen koppelen aan acute gezondheidseffecten zoals ziekenhuisopnames, ademhalingsklachten, cardiovasculaire incidenten en vroegtijdige sterfte, als in lange-termijnstudies, die chronische gezondheidseffecten onderzoeken in individuen die gedurende maanden tot jaren aan luchtverontreiniging zijn blootgesteld. Beide typen studies zijn essentieel om de volledige impact van luchtverontreiniging op de volksgezondheid te begrijpen en om beleid effectief te kunnen onderbouwen.

Het onderzoek dat in dit rapport wordt beschreven richt zich op de relatie tussen verhoogde dagelijkse luchtverontreiniging en acute sterfterisico's. Het rapport bestaat uit drie delen:

1. Een evaluatie van de omvang van dagelijkse sterfte door dagelijkse luchtverontreiniging (acute effecten) in Nederland in de periode 1995-2019, met als doel te beoordelen of het gevoerde beleid om de luchtkwaliteit te verbeteren effectief is geweest.
2. Een beoordeling met de zogenaamde 'gemiddelde-risicobenadering' of de omvang van acute gezondheidseffecten door dagelijkse luchtverontreiniging voor toekomstige jaren en scenario's op een eenvoudige manier kunnen worden gemodelleerd.
3. Een verkenning naar of en hoe onderzoek naar hoog-risico groepen en hoog-risico locaties voor acute effecten van dagelijkse luchtverontreiniging vorm kan worden gegeven.

De resultaten worden hieronder per deel beschreven.

Deel 1: Omvang van dagelijkse sterfte door dagelijkse luchtverontreiniging in Nederland in de periode 1995-2019

In deel 1 (hoofdstuk 2) van de studie is onderzocht of de omvang van dagelijkse sterfte door fluctuaties in dagelijkse luchtverontreiniging in Nederland tussen 1995 en 2019 is veranderd. Internationaal en eerder in Nederland uitgevoerd epidemiologisch onderzoek laat verbanden zien tussen kortdurende verhoogde blootstelling (maximale 8 uurs gemiddelde of 24- uursgemiddelde concentratie) aan luchtverontreiniging en een toename van zowel de totale sterfte als van doodsoorzaak-specifieke sterfte aan hart- en vaatziekten en ziekte van de luchtwegen en de longen.

Het doel van deze studie is om te onderzoeken of de risico's om te overlijden aan luchtverontreiniging gedurende een tijdsperiode van 25 jaar (1995-2019) zijn veranderd als gevolg van de veranderingen in concentratieniveaus en in de samenstelling (als gevolg van bijv. luchtkwaliteitsbeleid) en daarmee mogelijk gepaard gaande verandering

in de toxiciteit van het luchtverontreinigingsmengsel. Als eindjaar is 2019 gekozen, zodat de mogelijke invloed van de Covid-19 epidemie op de resultaten wordt vermeden.

Hiervoor zijn de extra risico's (ER's) om te overlijden aan luchtverontreiniging (fijnstof: PM10, PM2,5, stikstofdioxide: NO_2 en ozon: O_3) onderzocht voor verschillende tijdsperiodes: 1995-1999, 2000-2004, 2005-2009, 2010-2014 en 2015-2019. Voor PM2,5 zijn de sterfterisico's alleen onderzocht voor de periodes 2010-2014, 2015-2019, omdat PM2,5 pas vanaf 2008 is gemonitord. Met de ER's zijn de relatieve effecten van luchtverontreiniging op sterfte onderzocht. Verder is het totaal aantal doden bepaald (absoluut effect) dat in deze periode toe te schrijven is aan luchtverontreiniging ('attributive number'=AN).

Resultaten
De belangrijkste resultaten die uit het onderzoek naar voren komen zijn:

- Het Nederlandse luchtbeleid is effectief behalve voor ozon. Tussen 1995 en 2019 zijn de PM10 en PM2,5 en NO_2 concentraties gedaald in Nederland. O_3 concentraties stegen licht. De bevindingen uit het onderzoek geven aan dat het Nederlandse beleid met betrekking tot het verbeteren van de luchtkwaliteit in de afgelopen 25 jaar, uitgezonderd voor O_3, effectief was, omdat een vermindering van de concentraties fijnstof en stikstofoxiden daadwerkelijk tot een vermindering in het absoluut aantal doden door deze componenten leidde. Desondanks wijzen de bevindingen nog steeds op een verhoogd sterfterisico bij kortdurende blootstelling. Verwacht wordt dat een verdere verlaging van de concentraties zal leiden tot een verdere afname van de aan luchtverontreiniging toe te schrijven omvang van de dagelijkse sterfte.
- Ozon is een aandachtpunt voor de komende jaren. Ten eerste omdat O_3 concentraties afgelopen decennia licht zijn gestegen Daarnaast neemt de relatieve bijdrage van ozon aan de totale omvang van dagelijkse sterfte door kortdurende blootstelling toe, doordat de concentraties van PM10, PM2,5 en NO_2 zijn gedaald. Om verdere gezondheidswinst te boeken wordt het daarom steeds relevanter te kijken naar de effecten van ozon, en de mogelijkheden van vermindering van de blootstelling aan ozon.
- Er zijn geen aanwijzingen voor een toename van de toxiciteit van fijnstof over de beschouwde periode van 25 jaar op basis van dit onderzoek naar trends in effectschattingen; de periode-specifieke ER's voor fijnstof of ozon stegen niet (consistent) gedurende de tijd. Het sterfterisico voor NO_2 lijkt te zijn gedaald. We weten nog niet precies waardoor dit komt. Omdat NO_2 zelf niet van samenstelling verandert kan dit wijzen op een afname van andere schadelijke verbrandingsproducten dan NO_2, zoals roet of ultrafijne deeltjes (UFPs).

Regelmatige periodieke analyses van de trends in relatieve risico's kan worden gezien als een monitoringsactiviteit waarmee een vinger aan de pols kan worden gehouden met betrekking tot de gezondheidsrisico's van het luchtverontreinigingsmengsel en de daaraan gerelateerde toxiciteit van het mengsel van verschillende luchtverontreinigingscomponenten. Regelmatige periodieke monitoring

zorgt er ook voor dat de beleidsbeslissingen kunnen worden gebaseerd op de meest recente wetenschappelijke kennis en analysetechnieken. Verder kunnen de resultaten uit de monitoringsactiviteiten o.a. worden gebruikt als onderbouwing van beleidstools zoals bijvoorbeeld de Luchtkwaliteits Index (LKI). Deze LKI is momenteel in revisie.

Een volgende stap is het uitbreiden van de analyses door het berekenen van het effect van blootstelling aan meerdere componenten tegelijkertijd (multi-pollutant modellen), en ook te kijken naar effecten op morbiditeit (bijv. ziekenhuisopname, luchtwegklachten en medicatiegebruik in patiëntgroepen) en de tijdsreeks met een meer recente tijdperiode uit te breiden. De huidige analyses zijn gebaseerd op dagelijkse sterftecijfers, vanwege hun betrouwbaarheid en precisie in registratie.

Deel 2: Kan de omvang van de acute gezondheidseffecten door luchtverontreiniging voor toekomstige jaren *eenvoudig* worden geschat?

Om de omvang van acute gezondheidseffecten (zoals vroegtijdige sterfte, ziekenhuisopname en luchtwegklachten bij patiënten) in een kalenderjaar te modelleren zijn dagelijkse concentraties van fijnstof, NO_2 en O_3 nodig. Om in de toekomst in te kunnen schatten hoe de ziektelast van luchtverontreiniging zich ontwikkelt of om scenario's door te rekenen is het wenselijk een eenvoudigere werkwijze ter beschikking te hebben, omdat de modellering van dagelijkse concentraties op basis van emissies een extra inspanning vergt ten opzichte de berekening van jaargemiddelde concentraties.

Er is geëvalueerd of het mogelijk is om een "gemiddelde risicobenadering" toe te passen waarbij alleen de jaargemiddelde concentratie wordt gebruikt, en wat de toepassing van deze werkwijze betekent voor de nauwkeurigheid van de omvang van de acute gezondheidseffecten ten opzichte van het gebruik van dagelijkse concentraties. Deze evaluatie is op twee manier uitgevoerd: 1) een vergelijking van berekeningen met concentraties fijnstof, NO_2 en O_3 van achtergrondstations van het LML in de periode 2015-2019 en 2) met een simulatiestudie waarin verdelingen van dagelijkse concentraties zijn gegenereerd. Er is hierbij gekeken naar dagelijkse sterfte, spoedopnames in het ziekenhuis voor astma en naar luchtwegklachten bij patiënten.

Resultaten
De bevindingen laten zien dat de "gemiddelde risicobenadering" goed bruikbaar is voor berekeningen van de omvang van de acute gezondheidseffecten door kortdurende blootstelling in (toekomstige) scenario's. Hiermee kan de ontwikkeling van de ziektelast door luchtkwaliteit worden ingeschat. Deze benadering leidt weliswaar tot een kleine onderschatting van de omvang, maar deze onderschatting is beperkt bij de huidige en bij lagere luchtverontreinigingsconcentraties en bij aannames over de dagelijkse variatie in luchtkwaliteit zoals die in het verleden optrad.

Deel 3: Verkenning onderzoeksmogelijkheden hoog-risico groepen en hoog-risico locaties

Inzicht in factoren die van invloed zijn op de acute gezondheidsrisico's van kortdurende blootstelling aan luchtverontreiniging is cruciaal voor het vaststellen van effectieve maatregelen om de consequenties voor de gezondheid van blootstelling aan luchtverontreiniging te verkleinen. Deze informatie is daarnaast van belang voor het verbeteren van waarschuwingssystemen zoals de Luchtkwaliteitsindex (LKI) en voor instrumenten die zowel burgers als professionals op gebiedsniveau van informatie voorzien, waaronder de Atlas Leefomgeving.

Het aantal onderzoeken naar het potentiële effect van modificerende factoren is beperkt, met uitzondering van het aantal onderzoeken naar de rol van leeftijd en geslacht.
Het doel van dit deelonderzoek is om te verkennen wat er aan epidemiologisch onderzoek nodig is om de hoog-risico-groepen en hoog-risico omgevingen wat betreft acute effecten van luchtverontreiniging te identificeren en om vervolgens stappen te maken om deze "op de kaart" te zetten, zodat mogelijkerwijs in de toekomst communicatie over acute risico's meer kan worden toegesneden op aanwezige hoog-risico groepen en/of hoog-risico locaties. Inzicht in welke bevolkingsgroepen verhoogde gezondheidsrisico's lopen is essentieel voor het gericht ontwikkelen van interventies, het versterken van preventiebeleid en het bevorderen van de volksgezondheid.

Aan de hand van een literatuuronderzoek zijn zogeheten effect modificerende factoren geïnventariseerd die invloed kunnen hebben op het verband tussen dagelijkse concentraties luchtverontreiniging en acute gezondheidsrisico's. Effectmodificatie houdt in dat het verband tussen een bepaalde risicofactor, zoals luchtverontreiniging, en gezondheidsrisico niet gelijk is voor elke groep; bijvoorbeeld de relatie tussen luchtverontreiniging en sterfte kan sterker zijn onder oudere mensen dan voor jongere mensen. Inzicht in effectmodificatie helpt om te bepalen welke groepen het meest worden beïnvloed door een risicofactor. Vervolgens zijn de mogelijkheden verkend om deze risicofactoren te kwantificeren, door ruimtelijke koppeling van aanwezige databases over dagelijkse mortaliteit en morbiditeit aan bestaande databases over dagelijkse concentraties en aan relevante datasets met (individuele) gegevens over demografie, gezondheidsstatus, fysieke omgeving en buurt.

Er is een verkenning uitgevoerd met een populatie van overledenen die gestorven waren in de periode 2013-2019, waarbij gekeken is of bepaalde risicofactoren vaker of minder vaak voorkomen onder de overledenen op dagen met hoge concentraties O_3 dan onder overledenen op de overige dagen van de onderzoeksperiode.

Resultaten
De verkennende analyses leveren aanwijzingen op van effectmodificatie van het risico van kortdurende blootstelling aan O_3 door leeftijd, onderliggende ziekten (astma, COPD, hartritmestoornissen), inkomen en welvaart van het huishouden, en urbanisatiegraad. Kennis over effect-modificatie helpt om vast te stellen welke groepen of locaties het meest

getroffen worden bij verhoogde concentraties van een luchtverontreinigingscomponent.
De verkennende analyse laat zien dat op basis van bestaande data inzicht kan worden verkregen in effect-modificerende factoren. Voordat een grootschaliger vervolgonderzoek kan worden uitgevoerd is doorontwikkeling van de statistische methode nodig.

Aanbevelingen vervolgactiviteiten
Er worden een aantal aanbevelingen gedaan voor vervolgonderzoek.

- De omvang van acute sterfte door PM10 en NO2 is de laatste jaren gedaald en daardoor wordt het effect van acute blootstelling aan O3 steeds relevanter. Daarom wordt aanbevolen de kennis omtrent de acute effecten als gevolg van blootstelling aan O3 te vergroten.
- Om het effect van luchtverontreiniging op de gezondheid te bepalen wordt vaak gekozen voor een zogenaamd één-component model, wat kan leiden tot een onderschatting van de totale gezondheidsimpact. Aanbevolen wordt om te kijken wat het effect van blootstelling aan meerdere componenten op de gezondheid is, zodat de effecten kunnen worden uitgesplitst naar de verschillende luchtverontreinigingscomponenten. Deze kennis is relevant voor het selecteren van (kosten)effectieve maatregelen om luchtverontreinigingsconcentraties te verminderen.
- Klimaatverandering heeft geleid tot veranderde weerspatronen, wat weer invloed heeft op blootstelling aan luchtverontreiniging, extreme temperaturen en aeroallergenen, zoals pollen. Deze factoren kunnen synergistische effecten hebben op gezondheidsuitkomsten. Daarom is het wenselijk om te onderzoeken hoe gecombineerde kortdurende milieublootstellingen elkaar en de gezondheid beïnvloeden.
- Onderzoek wat de invloed is van demografische en sociaaleconomische kenmerken op de relaties tussen luchtkwaliteit en gezondheid zodat projecties van de resultaten naar de toekomst verbeterd kunnen worden en ook geëvalueerd kan worden of het wenselijk is dat in “early warning” systemen zoals de Luchtkwaliteitsindex of de smogalarmering onderscheid naar gevoeligheid van personen moet worden gemaakt.
- Verdere ontwikkeling van statistische methodes om acute gezondheidsrisico's van dagelijkse concentraties naar een klein-gebiedsniveau te projecteren, rekening houdend met demografische, sociaaleconomische, huisvestings-, buurt- en gebiedskenmerken, om discussies met lokale en regionale belanghebbenden over de acute effecten van luchtverontreiniging te vergemakkelijken.
- Voer, naast de effecten op sterfte, aanvullende analyses uit van luchtverontreiniging op morbiditeitsgegevens zoals ziekenhuisopnames en naar luchtwegklachten in patiëntgroepen.
- Her-analyseer de trends in associaties elke vijf jaar om mogelijke veranderingen in associaties tussen kortdurende blootstelling aan luchtverontreiniging en gezondheid en mogelijke veranderingen in de luchtverontreinigingsmengsel te evalueren. Dit zorgt er ook voor dat effectschattingen die worden gebruikt gebaseerd zijn op

de meest recente literatuur en dat statistische methodes worden toegepast volgens de laatste analysetechnieken.

- Rapporteer jaarlijks over de omvang van acute effecten als gevolg van kortdurende blootstelling aan een aantal luchtverontreinigingscomponenten, zoals tot 2014 werd gedaan in het Milieu Compendium, en zoals momenteel mogelijk is via het Compendium voor de Leefomgeving (CLO).

1 Introduction

Exposure to pollutants, such as airborne particulate matter (PM), nitrogen dioxide (NO_2) and ozone (O_3), has been associated with a wide range of health effects. These effects have been demonstrated in both short-term studies, which examine variation in exposure from one hour to days in relation to acute health effects, such as increased hospital admissions, respiratory symptoms, cardiovascular events, and premature deaths, and in long-term studies, which investigate (chronic) health effects of cohorts as result of exposed individuals over months to years. Both are essential for understanding the full burden of air pollution and guiding policy.

This report presents the findings of three activities that have been carried out to investigate the attributable risks of variations in daily concentrations of air pollutants on daily mortality and health.

In **chapter 2**, an evaluation was conducted to ascertain the efficacy of the Dutch air quality policy in mitigating the health risks posed by air pollution. This was achieved by examining trends in the associations between daily concentrations of air pollutants and daily mortality, and by quantifying the number of deaths attributable to air pollution for the period between 1995 and 2019.

In **chapter 3**, we examined the feasibility of developing a simplified model to predict the burden of acute health effects of short-term exposure to air pollution for future years and scenarios. This was accomplished by means of the so-called ‘average-risk approach’, which is a method to estimate the population attributable fraction (PAF) by using annual average concentrations. Therefore, a comparison was made between the burden of acute health effects associated with daily concentrations of air pollutants and the burden associated with annual average concentrations. Furthermore, we investigated how different exposure distributions might affect bias with a simulation study and illustrated the applicability of the average-risk approach with a case study from the Clean Air Agreement.

In **chapter 4**, a pilot study was conducted to evaluate the epidemiological research necessary to identify high-risk groups and locations for acute health risks from short-term exposure to air pollutants. This may contribute to the enhancement of health-related prevention policies concerning air pollution.

In **chapter 5** we present the overarching conclusions derived from the three studies.

2 Part 1 Evaluation of trends in risks related to air pollution and daily mortality in The Netherlands over the period 1995 – 2019

2.1 Introduction

It is well known that short-term (daily) variations in exposure to air pollution is associated with an increased risk in daily total mortality, as well as specific causes of death such as due to cardiovascular- and respiratory diseases (EPA, 2019; Gezondsheidsraad, 2018; Orellano et al., 2020).

In the Netherlands, air quality policy has been implemented to reduce the health risks of exposure to air pollution. The effectiveness of this policy can be assessed in a direct accountability study. This involves analysing trends in associations between daily concentrations of various air pollution components and daily mortality rates. The goal is to determine whether changes in attributable risk occur and if observed changes aligns with changes in exposure levels. Most evaluations are carried out in indirect accountability studies in which the change in exposure levels is translated in changes in attributable risk by making use of an external exposure response relation. The underlying assumption in these indirect accountability assessment is that the toxicity of components does not change over time. Air pollution is a mixture of various substances, with each a potentially different toxicity, and the ratio of these different substances can differ between locations and in time due to the variation of sources with different emissions. For example, particulate matter consists of various chemical substances, such as metals, organic and inorganic carbon and secondary components formed from ammonia, nitrogen and sulfur oxides, which can vary geographically and temporally. Furthermore, a certain component may be an indicator for other components, such as nitrogen dioxide which is generated during fossil fuel combustion and may be an indicator of exposure to soot and/or ultrafine particles as well (EPA, 2019). Therefore, air pollution measures taken in the past may have changed the toxicity of the air pollution mixture, and therefore these measures may have been more or less effective than previously expected.

In 2005 it was calculated, that between 1992 and 2002 approximately 4,000 people in the Netherlands died prematurely each year due to daily fluctuations in air quality (Fischer, 2005). In order to quantify the effectiveness of the implemented air pollution policy and the attributed health impact as result of these measures in the Netherlands, the RIVM recommended in 1998 that associations between air pollution and daily mortality should be evaluated in a direct accountability study at least every 5 years (Fischer, 1998). The last evaluation by the RIVM on the effects of air quality on daily mortality was performed in 2011 (Fischer et al., 2015), which has led to a loss of insight in the effectiveness of the implemented air pollution policy. Renewed attention for health risks of short-term exposure is also necessary with regard to issues related to

ongoing difficulties in isolating the independent effects of individual pollutants, the availability of new methods to detect effect thresholds, and questions about the extent to which effects are restricted to frail members of the population.

The aim of this study was to evaluate whether the Dutch air quality policy is effective in mitigating the risks of short-term exposure to air pollution and if the emission reducing measures target the right components. This was done by studying trends in associations between daily concentration levels of air pollutants and daily mortality in the Netherlands based on data from 1995 until 2019. The specific aims of the present study are:

1. to estimate exposure-response associations between daily mortality and ambient concentrations of particulate matter parameters PM10, PM2.5 (particles with a 50% cut-off at an aerodynamic diameter 10µm and 2.5µm respectively), and the gaseous parameters nitrogen dioxide (NO_2) and ozone (O_3).
2. to quantify the daily excess mortality attributable to short term air pollution variation.
3. to evaluate the results for 5-year periods (1995-1999, 2000-2004, 2005-2009, 2010-2014, 2015-2019) to detect trends in the relative risk estimates.

In section 2.2 the methods for data collection and analyses are described. The results are presented in section 2.3 and discussed in section 2.4. The conclusions are presented in section 2.5.

2.2 Methods

2.2.1 Data collection

Mortality data

Data on daily mortality counts for all causes of the complete Dutch population for the years 1995 – 2019 were obtained from the Statistics Netherlands (CBS). Due to the COVID-19 pandemic in 2020, it was decided not to include any data of the more recent years. Also, the daily mortality numbers were analysed by age group (0-64, 65-74, 75-84 and 85+ years), in order to take into account changes in the age distribution of the population over time. Also mortality data for two main causes: cardiovascular disease (ICD-10, codes I00-I99) and respiratory disease (ICD-10, code J00-J99) was collected. On July 17, 2014, Malaysia Airlines Flight 17 (MH17/MAS17) from Amsterdam to Kuala Lumpur was shot down over eastern Ukraine. All 298 people on board died, including 196 Dutch nationals. Therefore we removed this day from the dataset.

Air quality

Daily air pollution data for particulate matter (PM10 and PM2.5), ozone (O_3) and nitrogen dioxide (NO_2) were obtained as described by Fischer et al. (Fischer et al., 2011). Air quality data were collected from our institute, which operates the National Air Quality Measurement Network in the Netherlands (Van Elzakker, 2001). This network currently comprises approximately 50 monitoring sites in both rural and urban areas. Their mutual distance increases with decrease in population density. For the present study, we selected all rural and urban background monitoring stations where the air pollution component of

interest was measured as these stations are representative for the exposure of the general population. We excluded typical urban street monitoring stations, which are located at sites where the influence of local sources is considerable. The selected monitoring stations are located throughout the Netherlands. We used 24-hour average concentrations (midnight to midnight) for PM and NO_2. For O_3 the maximum 8-hour moving average per day was calculated. For PM2.5, measurements were available from 2008 onwards as monitoring started in 2008. Daily nationwide average concentrations for all components were calculated using all stations that measured the specific component. Missing values were imputed iteratively, using both the daily mean across all stations and the yearly mean for each station. Specifically, a missing value at station *s* on day *d* was estimated by calculating the mean concentration from all other stations for that day, and then multiplying this value by the ratio of the yearly mean at station s to the overall yearly mean for all stations. Appendix table A1 shows an overview of all monitoring stations that are included and the pollutants measured at these sites.

Meteorology
Mean daily temperature (in C°), relative humidity (in %) was obtained from the Royal Dutch Meteorological Institute (KNMI) as 24-hour average based on hourly measurements in The Bilt (station 260). As climate in the Netherlands is comparable across locations we considered one central measuring location.

Influenza A, B and respiratory syncytial virus
Data on weekly counts of virological data on influenza A, B and respiratory syncytial virus (RSV) were obtained from the Virological Weekly Reports. This is a surveillance system with real time viral infection data from a number of microbiological laboratories (~20) that are members of the Dutch Working Group of Clinical Virology (NWKV) and that is managed by the Centre for Infectious diseases Epidemiology of RIVM. These series are considered to track national respiratory pathogen trends, with varying pathogen coverage. Young children are likely overrepresented, but due to their robust reporting history spanning over three decades, these series are useful for tracking trends over an extended period. Data on weekly counts were converted into (moving average) daily counts.

Pollen
Data on airborne pollen counts have been obtained from two sites in the Netherlands; Helmond (Elkerliek Hospital) and Leiden (Leiden University Medical Center). Data collection procedures have been described elsewhere (Spieksma et al., 1985). Most of the pollen that are counted do not have allergic potential. As potential important allergens for our analyses we selected birch (Betula), grasses (Poaceae), and weeds[1]. The distributions of airborne pollen levels are highly skewed and therefore pollen were included as a categorical variable. Three categories were defined with cutoff-points a priori set at low (<10 grains/m^3), moderate (10-100 grains/m^3 for birch and 10-30 grains/m^3 for grasses and weeds), and abundant (>100 grains/m^3 for birch

[1] Weeds: Artemisia, Rumex, Plantago, Ambrosia or Urtica

and >30 grains/m^3 for grasses and weeds)(Jaakkola et al., 2021). When daily pollen counts were missing outside their specific pollen season, missing data is set to zero.

2.2.2 *Statistical analyses*

Health effects are expressed as excess risk (ER) in all-cause mortality for air pollution and the total daily number of deaths attributable to air pollution (AN). The ER show the relative effect of a pollutant and indicates how much the risk of health effects increases per fixed rise in the concentration (e.g. per 10 µg/m^3). Temporal variations in these associations may reflect changes in the toxicity of the air pollution mixture. The AN is an indicator of the absolute effect of a pollutant and shows the total number of deaths that can be attributed to exposure, it depends on actual concentration levels. This makes it a good indicator of policy effectiveness: if air pollution concentrations decrease due to regulations, the number of deaths attributable to air pollution will also decrease.

The analyses were performed with R software (version 4.4.2; (R Development Core Team; http://R-project.org)). Associations between all-cause mortality and PM10, PM2.5, NO_2 and O_3 concentrations were analysed using a standard time series approach using linear quasi-Poisson regression models, allowing for overdispersion. The methods of analysis were based on the studies performed by the Multi-Country Multi-City (MCC) Collaborative Research Network into the risk of air pollution (Chen et al., 2017; Liu et al., 2019; Meng et al., 2021; Vicedo-Cabrera et al., 2020) and adjusted for the situation in the Netherlands. For all pollutants, we used a 2-day moving average (lag 0 and 1) , i.e. the present and previous day concentrations. Consistent with the approaches used in previous studies the following covariates were included in the main model: (1) a natural cubic spline function of time (date) with seven degrees of freedom (df) per year to control for unmeasured temporal trends longer than 2 months in mortality, (2) an indicator for day of the week to account for short-term within week variations, (3) a natural spline function with 3 df for a 4-day moving average (lag 0 to 3 days) of temperature and with 3 df for relative humidity of the present day (lag 0) in order to exclude potential nonlinear and lagged confounding effects of weather conditions, (4) national holidays and (5) weekly counts of influenza A, B and RSV. For O_3 we applied a stricter control for temperature, and used the method as previously described by Stafoggia et al. (Stafoggia et al., 2009). We used a natural spline with 2 knots located at the 75th and the 90th percentiles of the distribution of the 2-day moving average (lag 0-1 days) to model warm temperatures. For cold temperatures a natural spline fixed on the 25th percentile distribution of the 6-day moving average (lag 1-6 days) was used. In addition, the shape of the exposure-response curve between air pollution and mortality was evaluated by using natural splines with 3 degrees of freedom.

Regression coefficients and standard errors were transformed into the percentage excess relative risk estimates (ER=100*(RR-1)) and 95% confidence intervals for mortality relative to an increase in pollutant concentration of each pollutant of 10 µg/m^3.

Next, the health impact was assessed from the risk estimates derived from the exposure response associations, by computing the number of excess deaths attributable to exposure to air pollution (attributable

number; AN) by a methodology to estimate health impact measures as described elsewhere (Vicedo-Cabrera et al., 2019).

Age-specific associations
As exposure-response associations between air pollution and mortality might differ per age group, we first performed exposure response analyses for four different age classes: 0–64, 65–74, 75–84, 85+ years. We used the best linear unbiased predictions (BLUPs) method to obtain unbiased predictions for age-specific associations. BLUPs represents a trade-off between (e.g. time- or location-) specific estimates and the pooled mean, shrinking the former to the latter (Sera et al., 2019; Sera & Gasparrini, 2022).

Trends
Exposure-response associations were analysed for the total period from 1995 to 2019, as well for 5 non-overlapping time intervals of 5 years for PM10, NO_2 and O_3. As PM2.5 was measured since 2008, for PM2.5 associations were only calculated for the intervals 2010-2014 and 2015-2019. Length of the time intervals was chosen a priori, to derive sufficient statistical power to analyse period-specific estimates, and sufficient time points to detect variability over time.
To study temporal changes in the association between air pollution and mortality, period-specific estimates were modelled using longitudinal random effect meta-regression (Sera & Gasparrini, 2022). Time, defined as midpoint-year of each 5-year time interval, was included as a linear fixed term, and the estimate derived from this model, that can be interpreted as the change in mortality risk associated with a change in time of every 5-year time interval, was used to predict the linear trend between each component and mortality for the period between 1995 and 2019. Next, the period-specific estimates were improved with obtaining the BLUPs of the trend estimate.

Sensitivity analyses
To study the robustness of the results we performed several sensitivity analyses. We assessed the association between air pollution and mortality using the same models as were used by MCC:

- For PM: exposure lag 0-1, confounder model: 1) a natural cubic spline function of time with seven degrees of freedom (df) per year; 2) an indicator day-of-week; 3) a natural spline function with 6 df for temperature (moving average of lag 0-3); 4) 3 df for relative humidity (lag0)
- NO2: exposure lag 1, confounder model: 1) a natural cubic spline function of time with 7 df per year; 2) an indicator day-of-week; 3) a natural spline function with 6 df for temperature (moving average of lag 0-3); 4) 3 df for relative humidity (lag0)
- O3: exposure lag 0-1, confounder model: 1) a natural cubic spline function of time with 7 df per year; 2) an indicator day-of-week; 3) distributed lag non-linear models over lag 0-21 for temperature

In addition, we evaluated the possible role of pollen. For pollen a 4-day moving average (lag 0-3 days) was used. Also, associations were investigated with cardiovascular and respiratory mortality.

2.3 Results

2.3.1 Data description

Descriptives of exposure, covariates and outcomes

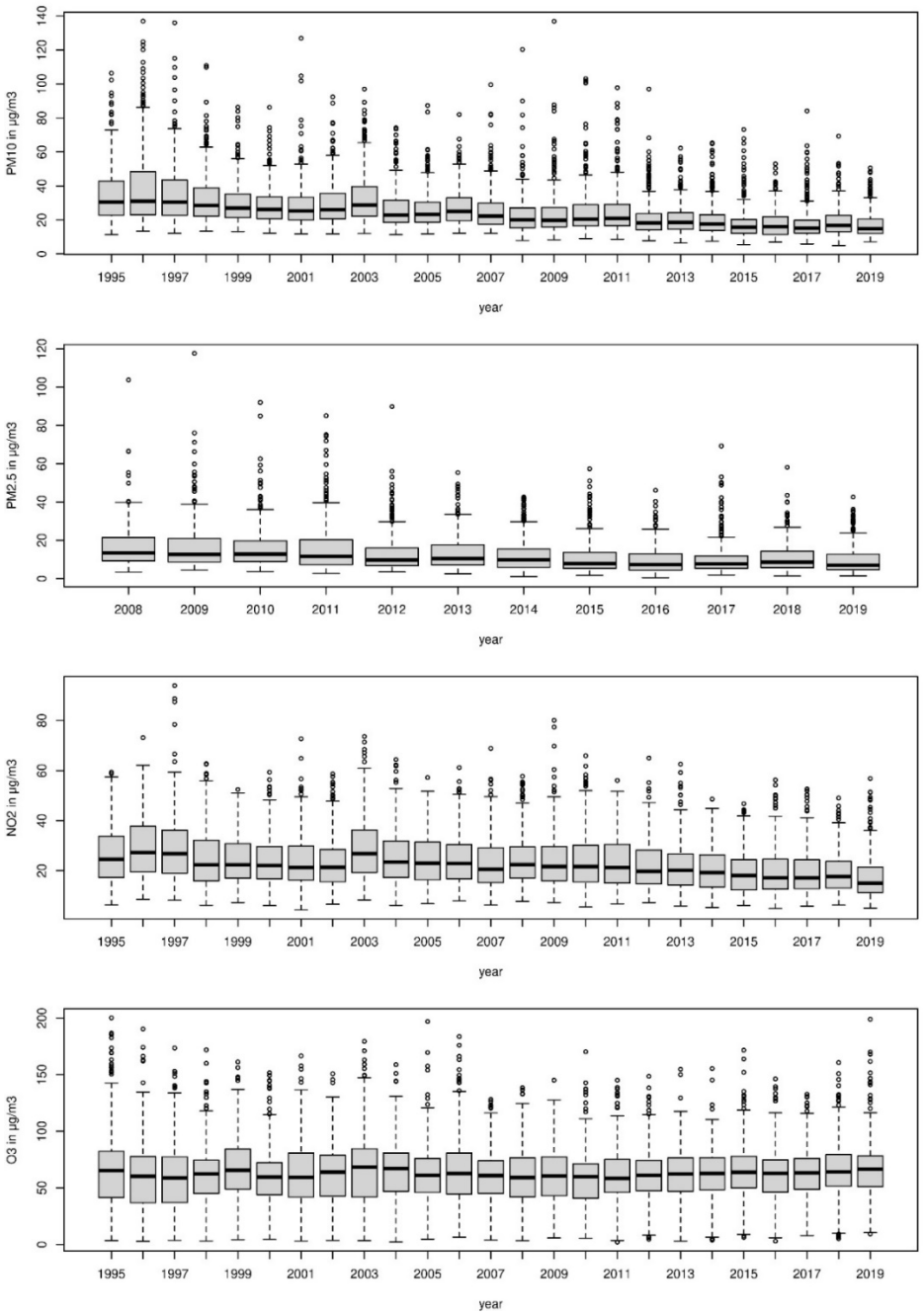
Table 2.1 shows the summary statistics of mortality, influenza counts, pollen and meteorological conditions for the complete study period and figure 2.1 shows the trend in annual average air pollution concentrations between 1995 and 2019 per component. On average, 384 persons died daily during the complete study period. Approximately 1/3 of these deaths were related to cardiovascular mortality and ~10% was related to mortality of the respiratory tract. Birch and weed pollen concentrations were low in more than 90% of the days in the period 1995-2019, while grass pollen concentrations were low in ~80% of the days (see Appendix Table A2).

Table 2.1 Overall summary statistics of key variables, 1995-2019.

Variable	**Mean**	**Min**	**P10**	**P90**	**Max**
Mortality - total (per day)	384	272	335	440	610
Mortality – cardiovascular (per day)	118	53	91	147	220
Mortality – respiratory (per day)	36	10	23	52	113
Influenza A (no. weekly positive laboratory diagnoses)	0.21	0	0	0.4	7.6
Influenza B (no. weekly positive laboratory diagnoses)	0.07	0	0	0.08	5.7
RS-virus (no. weekly positive laboratory diagnoses)	0.29	0	0	0.9	2.4
Particulate matter, PM10 (24-average in µg/m^3)	25.8	4.9	13.0	43.3	137.0
Particulate matter, PM2.5 (24-h average in µg/m^3)	13.1	0.5	4.5	25.5	117.7
Nitrogen dioxide, NO_2 (24-h average in µg/m^3)	23.5	4.4	11.6	38.7	93.9
Ozone, O_3 (8h-max in µg/m^3)	62.3	2.1	25.8	94.6	200.2
Daily average temperature (°C)	10.6	-12.6	2.2	18.5	29.7
Relative humidity (%)	81	31	68	93	100

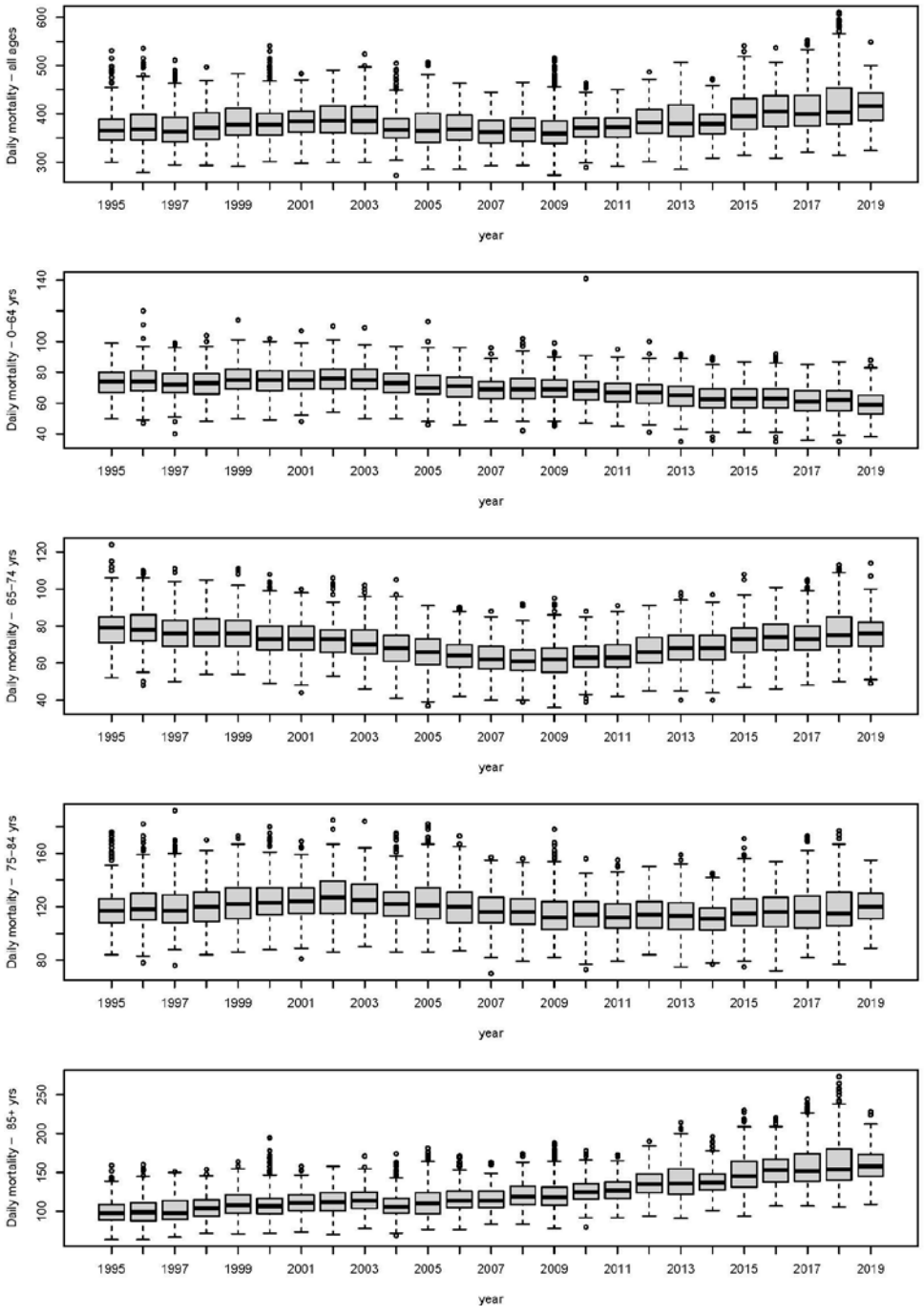
Between 1995 and 2019 levels of PM10 and NO_2 decreased considerably, with a decline of approximately 50% for PM10 and 33% for NO_2 (PM10: from 36 µg/m^3 to 17 µg/m^3, NO_2: from 26 µg/m^3 to 18 µg/m^3). PM2.5 levels decreased about 40% between 2008 and 2019 (from 17 µg/m^3 to 10 µg/m^3). Average ozone levels increased slightly during the study period of 25 years (from 66 µg/m^3 to 67 µg/m^3) (Figure 2.1).

Figure 2.1 Annual air pollution levels in the Netherlands between 1995-2019 in µg/m³. The horizontal lines in each box indicate the median; boxes represent the interquartile range (IQR), and whiskers extend to 1.5×IQR. Dots represent outliers.



Daily mortality levels increased during the study period (figure 2.2). Stratification of mortality by age category shows a strong increase in the oldest age category (85 years and older) and a decrease in the youngest age category (0-64 years)

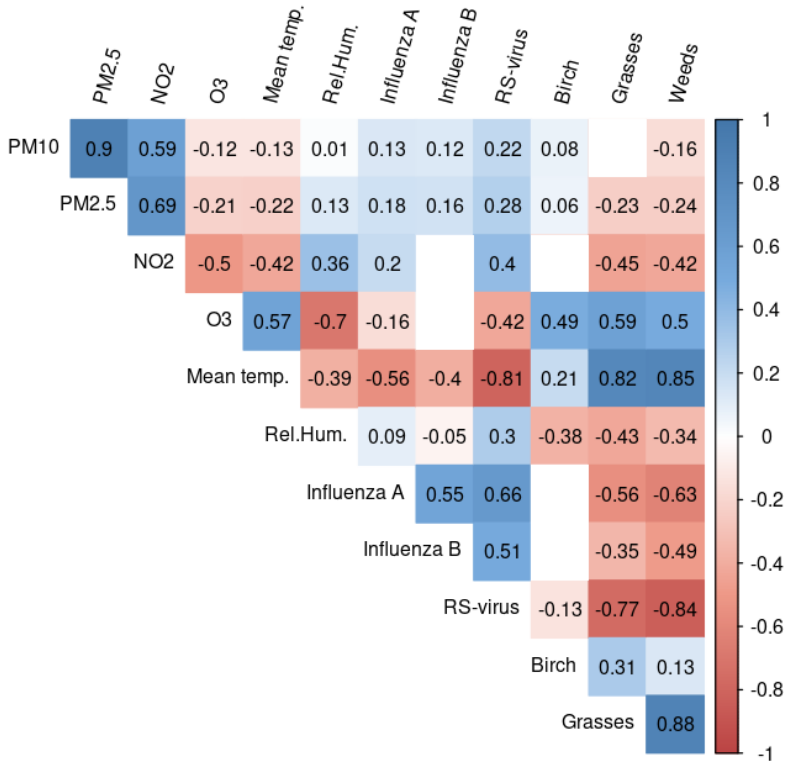
Figure 2.2 Average all-cause daily mortality counts per year in the Netherlands from 1995 to 2019.



Correlations

PM10 and PM2.5 were very strongly positively correlated (spearman correlation coefficient of r=0.9) and NO_2 and PM were strongly positively correlated (PM2.5: r =0.69 and PM10: r =0.59). There was a weak negative correlation between O_3 and PM (PM2.5: r =-0.21, PM10: r=-0.12) and a moderate negative correlation with NO_2 (r=-0.5) (Figure 2.3). O_3 was moderately positive correlated with temperature, birch, grass and weed pollen and negatively correlated with the average relative humidity and the RS-virus; an opposite pattern was found for NO_2.

Figure 2.3 Spearman correlation coefficients of air pollutants, meteorology, influenza, RS-virus and birch, grass and weed pollen in the Netherlands in the period 1995-2019.



2.3.2 *Associations between mortality and air pollution*

Associations with all-cause mortality for the complete study period

Table 2.2 shows the associations between air pollution and daily all causes or cause-specific mortality for the whole study period 1995-2019. For the overall period positive associations were found between the various air pollutants and all causes and respiratory and cardiovascular daily mortality. All excess relative risk estimates (ERs) were greater than 0. All-cause mortality was strongest associated with NO_2; an average increase in 10 µg/m^3 NO_2 of the current and previous day (i.e. a moving average of lag0-1) resulted in an estimated mortality increase of 0.49% in the period between 1995-and 2019. An 10 µg/m^3 increase in PM10 and O_3 resulted in an increase of mortality of 0.37% and 0.26% respectively. For PM2.5, we found an 0.18% increase in all-cause mortality per 10 µg/m^3 between 2008 and 2019.

Table 2.2 Overall daily all-cause mortality risk for the period 1995-2019 associated with a 10 µg/m³ increase in air pollutant concentrations (lag 0-1) expressed as percentage excess risk estimates (ER) and 95% confidence intervals (CI) and number of deaths per year attributable to air pollution.

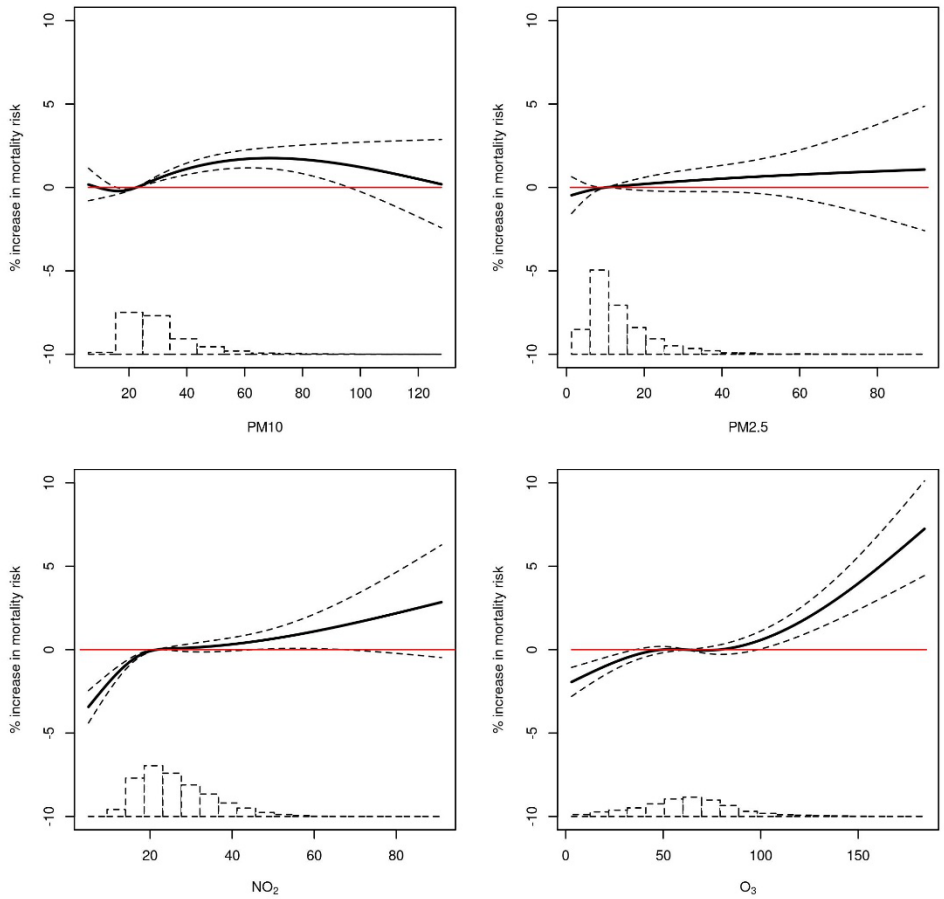
Pollutant	All causes ER (95% CI)	AN (95% CI)[4]
PM10[1]	0.37 (0.24, 0.50)	1333 (857,1786)
PM2.5[1,2]	0.18 (-0.05, 0.41)	161 (0, 370)
NO_2[1]	0.49 (0.31, 0.67)	1616 (1006, 2197)
O_3[3]	0.26 (0.16, 0.36)	2200 (1312, 3044)

[1] Associations were adjusted for time trends with a natural cubic spline function of time with seven degrees of freedom (df) per year, DOW and a natural spline function with 3 df for a 4-day moving average (lag 0 to 3 days) of temperature and with 3 df for relative humidity (lag 0), national holidays and weekly counts of influenza A, B and RSV
[2]Date from 1-1-2008 onwards
[3] Associations were adjusted for time trends with a natural cubic spline function of time with seven degrees of freedom (df) per year, DOW and with a 2-day (lag0-1) moving average for warm temperatures and the average of the previous six days (lag1-6) for cold temperatures, national holidays and weekly counts of influenza A, B and RSV
[4] Annual number of deaths attributable to air pollution component

Figure 2.4 presents the shape of the exposure-response curve between air pollution and all-cause daily mortality. For all pollutants mortality risks increased with increased exposure levels. The exposure-response curves for NO_2, O_3 and PM2.5 did not show a clear threshold below which pollutant levels had no effect on daily mortality. For PM10, we did not find associations at the lower (<25µg/m³) and highest levels (>70µg/m³), although confidence intervals were wide indicating greater uncertainty at the very high and low end concentrations.

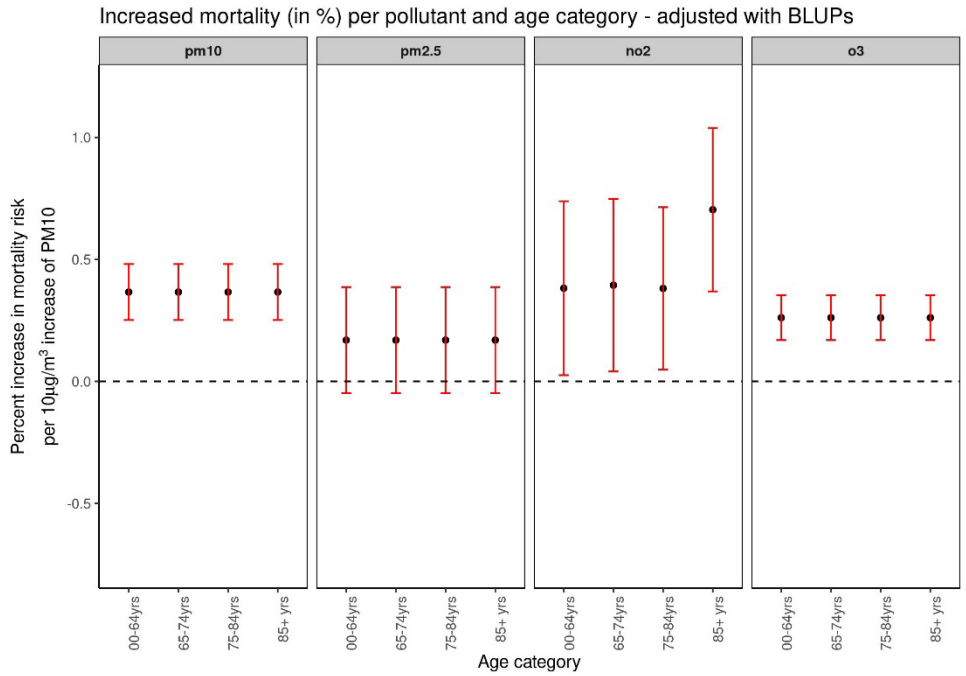
Associations between all-cause mortality and air pollution per age group
Associations between air pollution and mortality stratified per age group are shown in figure 2.5. The estimates did not show a difference in air pollution-mortality associations between age categories for PM10, PM2.5 and O_3. Only associations between NO_2 exposure and mortality were slightly stronger in the highest age category (85years+), compared to the other age categories. Therefore, we decided to use associations from the full-population models, instead of the age-stratified models to assess the temporal trends and health impacts of air pollution.

Figure 2.4 Non-linear exposure-response curves (including 95% confidence limits) for the association of 2-day moving average concentration of PM10, PM2.5, NO_2 and O_3 and daily all-cause mortality for the complete study period.



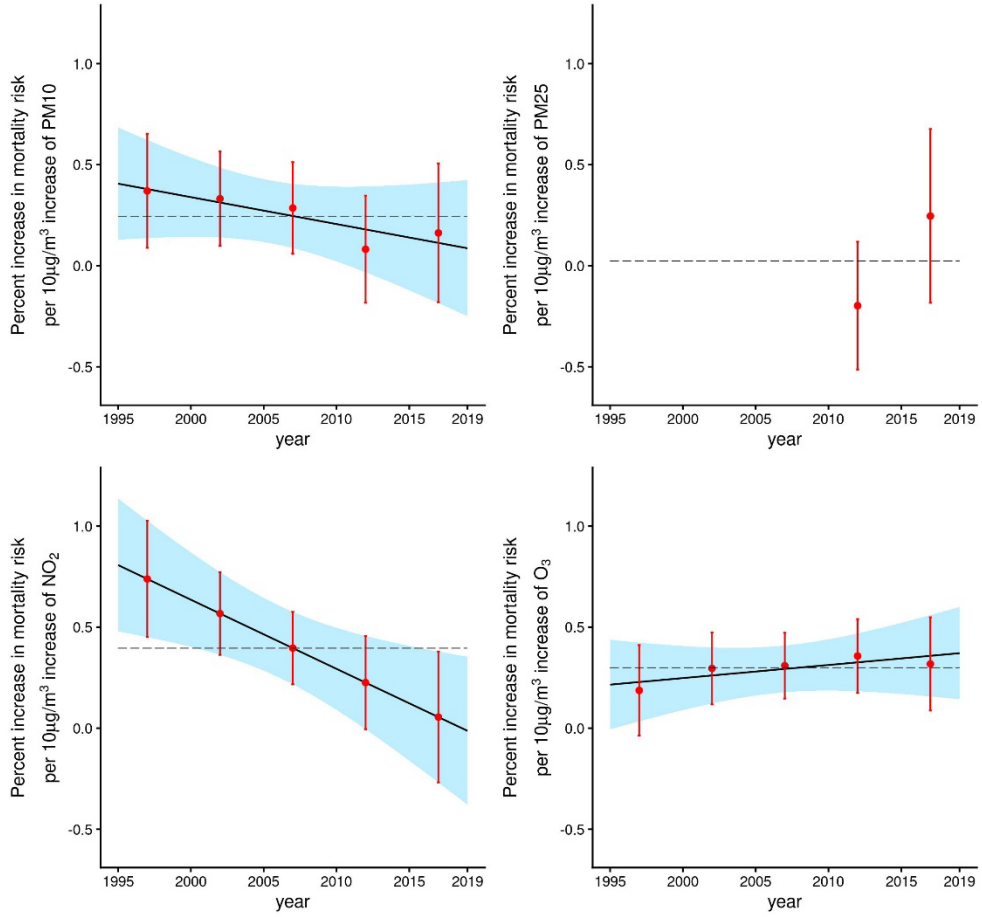
Associations with PM10, PM2.5 and NO_2 were adjusted for time trends with a natural cubic spline function of time with seven degrees of freedom (df) per year, DOW and a natural spline function with 3 df for a 4-day moving average (lag 0 to 3 days) of temperature and with 3 df for relative humidity (lag 0), national holidays and weekly counts of influenza A, B and RSV (only all-cause and cardiovascular mortality). For O_3, the same covariates were included, with the exception of temperature, where a moving average for warm temperatures and the average of the previous six days (lag1-6) for cold temperatures
For O_3, a stricter control of temperature was applied by using a 2-day (lag0-1) moving average for warm temperatures and the average of the previous six days (lag1-6) for cold temperatures.
Zero on the y axis (red line) represent no increase in mortality risk.
The histogram shows the distribution of concentrations of the specific air pollutant.

Figure 2.5 Increase mortality (in %) per pollutant and age category (predicted with BLUPs).



Associations between all-cause mortality and air pollution: per period
Figure 2.6 presents the associations between PM10, PM2.5, NO_2 and O_3 and all-cause mortality for each 5-year interval of the study period (red vertical error bars, including point estimate) and the temporal trend of the associations (black line). The width of the blue band indicates the indicates the uncertainty in the relationship. The black dashed line represents the increased risk of mortality for the complete study period. As for PM2.5 only associations were calculated for two 5-year-intervals (2010-2014 and 2015-2019), no temporal trend was estimated for this pollutant. The temporal trend for PM10 and NO_2 does not deviate statistically significantly from the effect estimate for the complete study period (black dashed line), which indicates that the excess relative risk estimates for air pollution mortality associations did not change in the Netherlands between 1995-2019. This suggests that the toxicity of the mixture did not change in more recent years. For NO_2, the temporal trendline decreased with ~3% per year (95%CI: -5% to -2%), from an estimated increase in mortality risk of 0.70% between 1995-1999 and 0.13% between 2015-2019.

Figure 2.6 Percent increase (95% confidence intervals (CI)) in total mortality associated with 10 µg/m³ increase in PM10, PM2.5, NO_2 and O_3 (lags 0–1 for all components) per 5-years and estimated temporal trend (black line and blue area) between 1995 and 2019 in the Netherlands.



The horizontal dashed line indicates the % increased mortality during the midyear of the study period. For PM2.5 the study period was too short to estimate the change in trend.

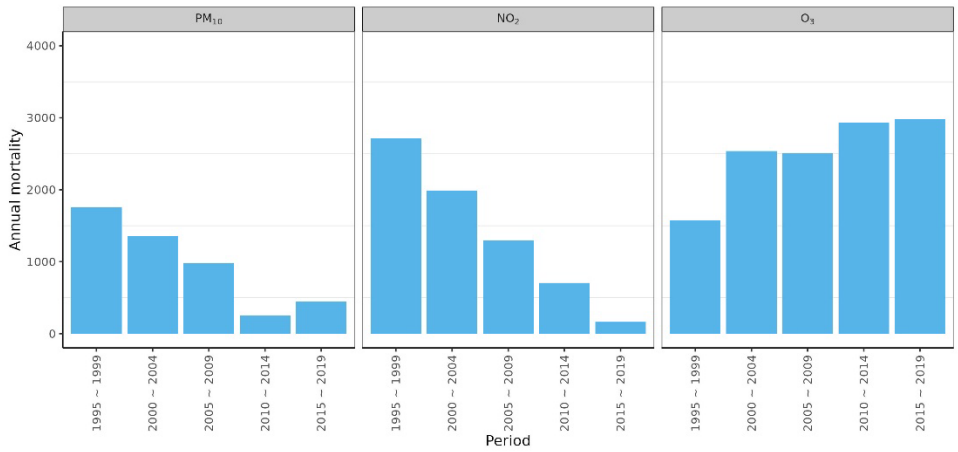
Number of deaths attributable to air pollution

Between 1995 and 2019, the estimated number of deaths per year due to air pollution were 1333 for PM10, 1616 for NO_2 and 2200 for O_3 (Table 2.2). Annually, 161 deaths were attributable to PM2.5 between 2008 and 2019 (Table 2.2). Although, the ER of O_3 is relatively low compared to the other pollutants, the total number of deaths attributable to O_3 is high. This can be explained by the difference in exposure distributions between components (table 2.1 and figure 2.1); daily O_3 concentrations are generally higher (on average 62 µg/m³) compared to daily PM10, PM2.5 and NO_2 concentrations (PM10 26 µg/m³, PM2.5 13 µg/m³, NO_2 23 µg/m³). The change in the total number of deaths attributable to air pollution during the study period, taking into account period-specific effect estimates, is shown in figure 2.7. A substantial number of annual excess deaths were attributable to exposure to air pollution. However, the estimated number of deaths per year due to PM10 and NO_2 decreased over time (between 2015 and 2019 to ~440 deaths per year for PM10 and ~160 deaths per year for NO_2). The estimated number of deaths attributable to O_3 increased and

became more relevant compared to the other components in the most recent years (~2980 deaths annual between 2015-2019). For PM2.5, no change in deaths attributable to air pollution was calculated. The temporal trend in associations was not informative, because effects of only two 5-years intervals can be included.

Figure A1 (Appendix 1) shows more insight in the total number of estimated deaths attributable to air pollution above and below the current WHO air quality standards. Almost all estimated deaths were caused by PM10, NO_2 and O_3 levels below the proposed WHO thresholds (from 2015-2019 for PM10: 99%, for NO_2 71% and O_3 98%). In case of NO_2, there were also a considerable number of estimated deaths caused by NO_2 above the threshold, although this was mainly the case for the earlier years (46% between 1995 and 1999 and 29% between 2015 and 2019).

Figure 2.7 Excess mortality per year associated with air pollution per component (PM10, NO_2 and O_3) and 5yr-time interval (1995-1999, 2000-2004, 2005-2009, 2010-2014, 2015-2019).



Sensitivity analyses

When the same confounder-models as MCC were used, associations were in general comparable to associations from our main model. For O_3, the use of the MCC model resulted in a lower effect estimate compared to the main model (ER 0.08 (95%CI -0.01-0.17) vs ER 0.26 (95%CI 0.16 – 0.36)) (table 2.3). This was mainly caused by including relative humidity in our model (estimate changed from ER 0.08 (95%CI -0.01, 0.17) to ER 0.20 (95%CI 0.10, 0.30)) and the stricter control for temperature in the confounder model used by MCC (estimate changed from ER 0.20 (95%CI 0.10, 0.30) to ER 0.25 (95%CI 0.15, 0.35)). Adjustments for pollen did not result in a change of associations between air pollution and mortality (table 2.3).

For cause-specific mortality (table 2.3), (significant) associations were only found between PM10 and respiratory mortality (ER 0.58 (95% CI 0.21-0.96)) and O_3 and cardiovascular mortality (ER 0.32 (95% CI 0.15-0.48)).

Table 2.3 Overall daily all-cause mortality risk diseases for the period 1995-2019 associated with a 10 µg/m³ increase in air pollutant concentrations expressed as percentage excess risk estimates (ER) and 95% confidence intervals (CI).

Model	PM10	PM2.5[1]	NO_2	O_3
Main model	0.37 (0.24, 0.50)	0.18 (-0.05, 0.41)	0.49 (0.31, 0.67)	0.26 (0.16, 0.36)
Sensitivity analyses				
MCC confounder model	0.36 (0.23, 0.48)	0.21 (-0.02, 0.45)	0.54 (0.38, 0.69)	0.08 (-0.01, 0.17)
Adjustment for pollen	0.35 (0.22, 0.48)	0.18 (0, 0.42)	0.47 (0.29, 0.65)	0.23 (0.13, 0.33)
Respiratory mortality	0.58 (0.21, 0.96)	0.52 (-0.18, 1.22)	0.29 (-0.24, 0.82)	0.25 (-0.06, 0.57)
Cardiovascular Disease mortality	0.12 (-0.08, 0.32)	-0.06 (-0.47, 0.35)	0.22 (-0.06, 0.51)	0.32 (0.15, 0.48)

[1]Date from 1-1-2008 onwards
[2]Associations were adjusted for time trends with a natural cubic spline function of time with seven degrees of freedom (df) per year, DOW and for a 7-day moving average (lag 0-6) of both temperature and relative humidity, national holidays and weekly counts of influenza A, B and RSV (only all-cause and cardiovascular mortality)
[3] Single pollutant models were not adjusted for PM2.5 as PM2.5 was not monitored before 2008 and 2-pollutant models should be compared with single pollutant model for the same period

2.4 Discussion

The main goal of this study was to evaluate whether the Dutch air quality policy is effective in reducing the health risks of exposure to air pollution. We studied trends in associations between air pollution and daily mortality, and assume that when these association (when expressed per fixed increment in concentration) change over time, this implies a change in the toxicity of the air pollution mixture as result of emission reducing measures. More specifically, this was addressed with following study aims:

- to estimate exposure-response associations between daily mortality and ambient concentrations of particulate matter (parameters PM10, PM2.5), NO_2 and O_3 for the Dutch population based on data from 1995 until 2019
- to quantify the daily excess mortality attributable to short term air pollution variation
- to evaluate the presence of trends in the relative risk estimates during the study period

Levels of PM10, PM2.5 and NO_2 decreased considerably between the period of 1995 and 2019 in the Netherlands, while O_3 levels increased slightly. We found no indications for a changed trend in associations between air pollution and daily mortality in the Netherlands during the study period 1995-2019. The estimated total number of deaths due to air pollution decreased over the same period. This indicates that Dutch air quality policy is effective, with the exception of ozone, in reducing risk for daily mortality due to short-term exposure. Nevertheless, the findings still indicate an increased risk from short-term exposure. It is expected that a further reduction in concentrations will lead to a further decrease in the attributable risks and the size of attributable daily mortality.

In the period between 1995 and 2019 we found overall statistically significant associations between PM10, PM2.5, NO_2, O_3 and daily mortality. Table 2.4 presents the effect estimates of the air pollution and mortality data from the Netherlands from the present study, together with the results from the systematic review that was commissioned by the WHO in order to generate evidence to support the latest update of the 2021 WHO air quality guidelines (AQGs) (Orellano et al., 2020). Also, the associations that were found in the studies that are conducted by the Multi-Country Multi-City (MCC) Collaborative Research Network were included. The MCC Network is an international collaboration of research teams working on a program aiming to produce epidemiological evidence on associations between environmental stressors, climate, and health (MCC, 2025).

Table 2.4 Overall daily mortality risk associated with a 10 µg/m³ increase in air pollutant concentrations: effect estimates of the analyses performed in the Netherlands, compared to the WHO-review and MCC studies.

Pollutant	Netherlands ER (95% CI)	WHO ER (95% CI)[2]	MCC ER (95% CI)
PM10	0.37 (0.24, 0.50)	0.41 (0.34, 0.49)	0.44 (0.39, 0.50)[3]
PM2.5[1]	0.18 (-0.05, 0.41)	0.65 (0.44, 0.86)	0.68 (0.59, 0.77)[3]
NO_2	0.49 (0.31, 0.67)	0.72 (0.59, 0.85)	0.46 (0.36, 0.57)[4]
O_3	0.26 (0.16, 0.36)	0.43 (0.36, 0.52	0.18 (0.12, 0.24)[5]

[1] Date from 1-1-2008 onwards
[2] (Orellano et al., 2020), [3] (Liu et al., 2019), [4] (Meng et al., 2021), [5] (Vicedo-Cabrera et al., 2020)

The magnitude of effect of PM10 on mortality in the analyses of the 25-year study period in the Netherlands was comparable with the associations that were found by the MCC (Liu et al., 2019) and the systematic review commissioned by the WHO. Associations between NO_2 and mortality were comparable with MCC (Meng et al., 2021), but lower than what was found in the WHO review. The observed estimate for O_3 was closer to the estimate of MCC (Vicedo-Cabrera et al., 2020) than to the estimate of WHO (Orellano et al., 2020).
Our PM2.5 effect was low, and not statistically significant (ER: 0.18% (-0.05-0.41%)). The effects that were found by MCC and WHO were considerably higher. The reason for this is not clear. Possibly, the relative low levels and variation in PM2.5 concentrations and the shorter observation time due to the later implementation of PM2.5 measurements result in reduced statistical power and wider confidence intervals.
The variations in the estimates of our study compared to the WHO and MCC-studies is likely caused by heterogeneity of associations between regions and time periods studied, driven by differing primary sources influencing particle composition, population characteristics, exposure patterns and model specification differences.
Effect estimates for air pollution and mortality were elevated but generally consistent when comparing exposure-response association between time periods, which suggest that the toxicity of the mixture did

not change in more recent years. For NO_2, the temporal trendline decreased. This can be the result of a reduction of other combustion-related products than NO_2 in the air pollutant mixture, such as an reduction in soot or ultrafine particles (UFPs). While the total number of deaths attributable to PM10 and NO_2 decreased considerably during the study period (between 2015-2019 annually ~450 to PM10 and ~160 to NO_2), the annual number of deaths attributable to O_3 was approximately 3,000.
A considerable part of all deaths were caused by air pollution levels below the proposed WHO thresholds. This implies that further improvement of air quality levels below the recommended WHO guidelines results in additional health benefits. Furthermore, results indicate that ozone has become an increasingly relevant air pollutant in the more recent years and considerable health benefits could be achieved if reduction of ozone levels are reached. In recent decades, the Netherlands and also other countries in the Europe Union have implemented successful air pollution policy to reduce the occurrence of smog episodes caused by O_3, resulting in reduced peak concentrations. However, average O_3 concentrations show an increasing trend. This is the result of rising global background O_3 levels, which forms a large part of the average concentration. Together with the expected climate change it is expected that O_3 levels will continue to rise without additional measures (RIVM, 2025). This emphasize that it is becoming more relevant to examine the drivers of concentration levels, possible mitigation measures and warning systems, and the health effects of ozone.
The magnitude of effects of PM10, NO_2 and O_3 on mortality is slightly more comparable with the results of the MCC-studies than with the results of WHO-review. RIVM is currently revising the Dutch Air Quality Index (AQI; in Dutch: LKI (Dusseldorp, 2015). In this process it will be discussed whether the exposure-response associations that result from the present trend analyses can be used for an update of the LKI, or that it is preferred to use an estimate that is based on data from multiple countries and that has been peer reviewed.

The current analyses are based on daily mortality data because of their reliability and accuracy in registration. Although mortality is studied most frequently, air pollution is also related to non-fatal disease endpoints, such as cardiovascular and respiratory morbidity. It is recommended to conduct additional analyses of morbidity data such as hospital admissions due to heart or lung conditions.

Most studies focus on the effect of exposure to a single pollutant. When the effect of a single-pollution model is used to represent the air pollution mixture the health impact can be potentially underestimated, as policy often affects the levels of multiple pollutants. On the other hand, simply adding effects of single-pollutant models results in double-counting as many pollutants are correlated because they are emitted by the same source (Chen et al., 2024; Gowers et al., 2020). Therefore, as next step we propose to examine associations of combined exposures (multi-pollutant model). In addition, we suggest to investigate a more recent proposed approach by using the combined O_3 and NO_2 oxidative capacity (NO_x) (Williams et al., 2014). This method accounts for the combined effects of both oxidants while addressing many of the

statistical challenges linked to two-pollutant models (Williams et al., 2014).

Besides exposure to multiple pollutants, combined/interaction effects of pollutants and climate-related exposures, such as temperature and pollen, are an upcoming research topic. There is evidence that temperature and pollen are associated with mortality (Brunekreef et al., 2000; Gasparrini et al., 2015; Jaakkola et al., 2021; Song et al., 2017) and one literature review (Anenberg et al., 2020) reported evidence of synergistic effects of air pollution, temperature and pollen. In the light of climate change, it becomes essential to study effects of combined exposures to air pollution, temperature and pollen. KNMI projections show higher temperatures in 2050 and 2100 in the Netherlands and it is unknown whether O_3 concentrations will continue to increase in the future.

The aim of our analyses was to study whether associations between air pollution and mortality have changed over time as result of changes in composition and the potentially associated changes in the toxicity of the air pollution mixture. Regular re-analyses of these trends in associations can therefore be regarded as a monitoring activity that helps keep track of the health effects of the air pollution mixture, which is of importance for justifying the implemented air quality policy aimed at measures to reduce emissions of pollutants.
We recommend to repeat analyses at intervals of approximately five years, in the first place to evaluate potential changes in associations between air pollution and health and potential changes of the air pollution mixture, but also in order to use the state-of-art-estimates by including the most recent literature and analyses techniques. Also, we recommend to update regularly a quantification of the size of the acute health effects attributable to short term air pollution, as was done up to 2014 in the Environmental Data Compendium (www.CLO.nl/nl034011).

2.5 Conclusions

- Between 1995 and 2019, the concentrations of PM10 and PM2.5 and NO_2 decreased in the Netherlands, while O_3 concentrations slightly increased.
- Throughout the entire period from 1995 to 2019, positive associations were found between daily variations in PM10, NO_2, O_3 concentrations, and daily variations in mortality rates.
- There were no indications of an increase in the toxicity of air pollution over time. Period-specific effect estimates (ERs) for particulate matter, nitrogen dioxide, and ozone did not show a upward trend.
- For NO_2, effect estimates appeared to decline. The reason for this remains unclear. As the chemical composition of NO_2 does not change, this finding could indicate a reduction on other combustion-related pollutants, such as soot or UFPs.
- The number of deaths attributable to air pollution decreased in the Netherlands between 1995 and 2019, except for O_3.

This indicates that the Dutch policies aimed at reducing the health risks due to short-term exposure by improving the air quality have been

effective over the past 25 years, except for ozone. Further reduction of concentration levels is expected to decrease the burden of attributable daily mortality. Additionally, these results indicate that ozone is playing an increasingly significant role in the disease burden of air pollution. It is, therefore, becoming more relevant to examine the effects of ozone. Regular periodic analyses of trends in relative risks can be considered a monitoring activity to keep track of potential changes in the health risks of the air pollution mixture.

3 Part 2 Prediction of the burden of health effects due to short-term exposure in scenarios for the future

3.1 Introduction

In the previous chapter, the burden of daily mortality due to short-term exposure to air pollution was estimated retrospectively for the period 1995-2019. There is a need to be able to estimate how the burden of acute health effects due to short-term exposure will develop in the future, for example in relation to climate change, or to calculate the burden for different scenarios as in the Clean Air Agreement (in Dutch: het Schone Lucht Akkoord) in addition to the burden of disease due to long-term exposure.
Daily concentrations of particulate matter (PM10, PM2.5) , nitrogen dioxide (NO_2) and ozone (O_3) at the location of background measurement stations are required to be able to model the burden of acute health effects in a calendar year. It would be desirable to have a simpler method. Modelling future daily concentrations based on emissions and weather requires more effort than calculating annual average concentrations, which are already modelled to assess the burden of disease from long-term exposure in scenarios for the future.

We have evaluated whether it is possible to use only the annual average concentration in order to estimate acute effects in relation to daily air pollution concentrations (the so-called average risk approach (IARC, 2007)), and what the use of this method means for the accuracy of the burden of acute health effects compared to the use of daily concentrations. This assessment was carried out in two ways:

- a comparison was made between the burden of acute health effects associated with daily concentrations of particulate matter, nitrogen dioxide and ozone from background stations of the national air quality monitoring network (in Dutch Landelijk Meetnet Luchtkwaliteit: LML), and the burden associated with the annual average of these daily concentrations from the LML and from large-scale concentration (GCN) maps in the period 2015-2019, and
- with a simulation study in which potential distributions of daily concentrations were generated, in order to investigate if the skewness of the exposure distribution affects the bias of the average risk approach.

Endpoints of interest were daily mortality, emergency hospital admissions for asthma and exacerbation of respiratory symptoms in adults with COPD.

In section 3.2, we introduce the concept of an 'average risk' approach and describe how the research was conducted. In section 3.3 we present the results and illustrate its applicability with a case study from the Clean Air Agreement. We finish in section 3.4 with a discussion and our conclusions.

3.2 Methods

The calculations of the burden of the acute health effects make use of the so-called population attributable fraction (PAF). The PAF and the average risk approach, and the steps to calculate the burden are described in Section 3.2.1.
The application of the average risk approach was evaluated for three different health endpoints. The selected exposure-response (E-R) relations are described in section 3.2.2.
The evaluation of the average risk approach is carried out with distributions of daily concentrations. This is done for PM10, PM2.5, NO_2 and O_3 with data from the LML in 2015, 2016, 2017, 2018 and 2019; with data from large-scale concentration (GCN) maps; with simulated exposure distributions and with an example from the Clean Air Agreement. The data sources and the way the simulated data were generated are described in sections 3.2.3 to 3.2.6.

3.2.1 Population attributable fraction and the average risk approach

In the previous chapter, the burden of acute effects was expressed as the (absolute) number of excess deaths attributable to exposure to air pollution (attributable number). In this chapter we use a similar but relative measure, the population attributable fraction (PAF). The PAF represents the proportion of a particular health outcome (or mortality) in the population that could be avoided if the exposure was completely eliminated. Like the attributable number of deaths, the PAF is an estimate of the theoretically achievable health gain in a population and is calculated for a calendar year from the risk estimate for the exposure-response (E-R) relation and the series of daily concentrations in that year. In the previous chapter, the risk estimate was the percentage excess relative risk (ER) estimate ($ER=100*(RR-1)$) which is based on the Relative Risk (RR). We will often use the RR itself as risk estimate in this chapter.

The calculation of the PAF for daily concentrations of a single air pollutant is performed in three steps.

1. Calculation of RR on day d based on daily concentration and RR per 10 µg/m^3 increase in daily concentration (c_d) as described in the literature or from the estimates derived in chapter 2:

   $$RR_d = \exp(\ln(RR) / 10 * c_d) \quad [1]$$

2. Calculation of relative risk increase (RRI) on day d:

   $$RRI_d = RR_d - 1 \quad [2]$$

3. Calculation of the PAF for the whole year using a weighted RRI:

   $$PAF_{year,d} = (\Sigma RRI_d / \Sigma days) / (1 + (\Sigma RRI_d / \Sigma days)) \quad [3]$$

It is assumed that the population size does not change during the calendar year and that everyone is exposed on all days, so that the weight of the daily RRIs is the same during the calendar year.

In 2007, a working group of the International Agency for Research on Cancer (IARC) presented an approach to estimate the PAF using the average of a continuous exposure distribution within a population and a RR from the literature (IARC, 2007). This *'average risk' approach* has subsequently been followed in several studies. The method can also be applied to a distribution of daily concentrations, which is demonstrated below.

The PAF calculated according to the average risk approach is based on the same RR as describe above and on the arithmetic annual mean of the distribution of daily concentrations of the same calendar year as above:

1. Calculation of RR for year y based on the arithmetic annual mean concentration (c_y) and the increase in the RR per 10 µg/m^3:

   $$RR_y = \exp(\ln(RR) / 10 * c_y) \quad [4]$$

2. Calculation of PAF for year y using a simplified Levin's formula (Levin, 1953):

   $$PAF_{year,y} = (RR_y - 1)/ RR_y \quad [5]$$

The average risk approach is attractive because it requires only the (annual) average exposure and simplifies the calculations to a simple situation where everyone is assumed to be exposed to the same concentration on all days of the year. It avoids the calculation of a PAF based on a polytomous exposure distribution, which is prone to error (Hanley, 2001).

Ruan et al. (Ruan et al., 2021) point out that no evidence of the validity of the method was provided by the IARC Working Group. It is likely that the magnitude of the risk estimate, the shape of the E-R relation, and the exposure distribution affect the validity of the method. The authors showed that when the RR is based on a log-linear risk assumption, which is the case in equation [1] and equation [4], the `average risk' approach will not overestimate the PAF. And if the RR per day is relatively small, the bias should be small. They specifically pointed out that when the exposure distribution is highly skewed, it is unclear whether the average risk approach still provides a good approximation of the underlying PAF.
In this chapter we therefore examine the validity and potential magnitude of bias of the average risk approach in the context of estimating the burden of health effects due to short-term exposure. We explore the effects of the magnitude of the RR and of the skewness of the exposure distribution.

3.2.2 E-R relations for selected health endpoints

Mortality

For mortality, we chose the E-R relations from the MCC studies because the risk estimates for PM10, NO_2 and ozone for the period 1995-2019 in the previous chapter are comparable with the results of these studies and because these studies considered so-called two-pollutant models (see below). The risk estimates expressed as ER are given in the last column of Table 2.4 in the previous chapter.

The daily concentrations of PM, NO_2 and O_3 are correlated, so the risk estimates for one pollutant may include part of the risk of another pollutant. The MCC publications investigated the role of co-exposure on the risk estimates for mortality. For PM, NO_2 had the largest effect; the risk estimates for PM reduced by about 35%. In a so-called two-pollutant model with NO_2, the RR for PM10 was 1.0028 (95% CI: 1.0022, 1.0035) and the RR for PM2.5 was 1.0042 (95% CI: 1.0031, 1.0053) per 10 ug/m^3 (Liu et al., 2019). Reversely, PM influenced the risk estimate for NO_2. In a two-pollutant model with PM10, the RR for NO_2 was 1.0038 (95% CI: 1.0026,1.0051) per 10 ug/m^3 (Meng et al., 2021). The RR of NO_2 with PM2.5 as co-pollutant was very similar, but in this chapter we will use the RRs adjusted with PM10 because of the better performance of PM10 over PM2.5 in the previous chapter. Also for O_3, we selected the risk estimate from a two-pollutant model with PM10. The RR for O_3 in this model was 1.0015 (95% CI: 1.0007, 1.0024) per 10 ug/m^3 (Vicedo-Cabrera et al., 2020). Where possible, we have also examined the bias of the average risk approach in the co-exposure situation. In such a situation we used the risk estimates from the two-pollutant models in addition to the estimates from Table 4.

When calculating the PAF of the combined exposure, the first step of the PAF calculation changes. Equation [6] replaces equation [1] when using daily concentrations and equation [7] replaces equation [4] when using the average risk approach.

1. Calculation of RR on day d based on daily concentrations and a RR_1 from a multi-pollutant model per 10 µg/m^3 increase in daily concentration ($c_{1,d}$) for component 1 and a RR_n from a multi-pollutant model per 10 µg/m^3 increase in daily concentration ($c_{n,d}$) for component n:

   $$RR_d = \exp(\ln(RR_1) / 10 * c_{1,d} + \ldots + \ln(RR_n) / 10 * c_{n,d}) \quad [6]$$

2. Calculation of RR for year y based on the arithmetic annual mean concentration ($c_{y,1}$) and the increase in the RR_1 from a multi-pollutant model per 10 µg/m^3 for component 1 and the arithmetic annual mean concentration ($c_{y,n}$) and the increase in the RR_n from a multi-pollutant model per 10 µg/m^3 for component n:

   $$RR_y = \exp(\ln(RR_1) / 10 * c_{1,y} + \ldots + \ln(RR_n) / 10 * c_{n,y}) \quad [7]$$

Emergency department visits and hospital admissions due to asthma
Table 3.1 shows the RR per 10 µ/m^3 for PM10, PM2.5, NO_2 and O_3 used for the analysis of emergency hospital admissions for asthma. These RRs are based on meta-analyses assuming a loglinear relation between the risk of emergency hospital admission and the daily concentration.

Table 3.1 Relative risks for emergency hospitalisation for asthma and daily 24-hour mean PM10, PM2.5 and NO_2 concentration and daily maximum 8-hour mean O_3 concentration and their 95% confidence interval.

Pollutant	RR per 10 µ/m^3	Reference
PM10	1.010 (1.008, 1.013)	(Zheng et al., 2015)
PM2.5	1.023 (1.015, 1.031)	
NO_2	1.0141 (1.0084, 1.0197)	(Zheng et al., 2021)
O_3	1.0082 (1.0053, 1.0111)	

The publication by Zheng (Zheng et al., 2021) notes that there were only a limited number of publications evaluating the influence of co-exposure. For O_3, the RR became smaller and was no longer statistically significant; for NO_2, no publications on the influence of co-exposure were available. In the older publication by Zheng (Zheng et al., 2015; Zheng et al., 2021), the influence of correction for co-exposure is not discussed for particulate matter. For this reason, we have limited the quantitative analyses for emergency hospitalisation for asthma to single pollutant examples.

Exacerbation of respiratory symptoms and additional bronchodilator use in adults with COPD

Increased concentration levels are also associated with exacerbation of respiratory symptoms and additional use of respiratory medications. The studies looking at these health outcomes are designed differently from those looking at mortality or emergency admissions and logistic instead of log-linear models are used for the statistical analyses.

We used the results of a panel study conducted in Wijk aan Zee to quantify the effects of short-term exposure to PM10 in adults with COPD (Dusseldorp et al., 1995) to explore the possible bias of the average risk approach. From the results of the publication, and with the help of one of the authors, E-R relations with 24-hour average PM10 concentrations were derived for several respiratory symptoms (see Figure 3.1).

Figure 3.1 shows that daily respiratory complaints occur even at low concentrations, which makes sense as the results were obtained from a population with pre-existing respiratory problems.

We restricted our analyses in this chapter to the symptoms with the highest and the lowest prevalence: `wheeze' and `bronchodilator use'. As the results in the panel study were obtained with a logistic regression model, the implementation of the calculations is different from that for mortality and emergency hospital admissions. We calculated an RR based on the prevalence at a given PM10 concentration and the 'baseline' prevalence (at a concentration of 0 ug/m^3), so that the next calculation steps are identical to those for a log-linear model (equations [2] and [3]).

1. Calculation of the prevalence (as proportion) (P) on day d in relation to the daily concentration PM10 ($PM10_d$) according to the following equations for wheeze and for bronchodilator use:

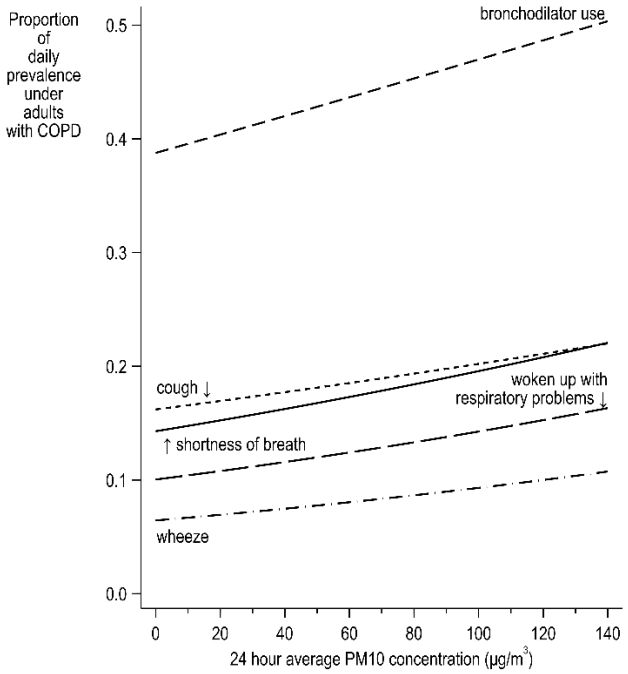
$$P_{wheeze,d} = (1 + \exp(-(-2.675 + 0.0400 / 10 * PM10_d)))^{-1} \quad [8a]$$

$$P_{brocho,d} = (1 + \exp(-(-0.457 + 0.0336 / 10 * PM10_d)))^{-1} \quad [8b]$$

2. Calculation of RR on day d:

$$RR_d = (P_{symp,d} - P_{symp,at\ 0)} / P_{symp,d} \quad [9]$$

Figure 3.1 Relations between daily 24-hour average PM10 concentration and the daily prevalence of a number of respiratory symptoms and the use of short-acting bronchodilators among adults with COPD (Dusseldorp et al. 1995).



3.2.3 *Daily and annual air pollution data used from the LML*

Daily air pollution data for PM10, PM2.5, NO_2 and O_3 were obtained from urban and rural background monitoring stations in the LML. The same data set was used as in the previous chapter.
For a (simple) comparison of the two calculation methods, daily nationwide average concentrations for all components were calculated for the calendar years 2015, 2016, 2017, 2018 and 2019 using all stations that measured the specific component. For PM and NO_2, 24-hour average concentrations (midnight to midnight) were used. For O_3, the maximum 8-hour moving average per day was calculated.
To evaluate the effect of skewness of the exposure distribution, we examined time series of daily concentrations for the period 1995-2019 (PM10, NO_2 and O_3) and for the period 2008-2019 (PM2.5). We calculated a daily average per part of the country (northern, eastern, western and southern Netherlands) instead of a daily average concentration for the whole country to get an insight into the variability of the skewness of the distributions. The results were used to simulate realistic exposure distributions (see section 3.2.5).

3.2.4 *Annual air pollution data used from GCN maps*

Since the average risk approach could potentially be used in future scenarios, we also used modelled concentrations of PM10, PM2.5, NO_2 and O_3 from large-scale concentration (GCN) maps for the calendar years 2015, 2016, 2017, 2018 and 2019. The maps provide a picture of

the annual average concentration at a resolution of 1 km by 1 km. The GCN maps are based on emissions from the emission register and model calculations(Mijnen-Visser, 2024).

We identified the locations of the background monitoring stations for each component. The maps were then combined to obtain an annual mean concentration for each station from the 1 km by 1 km grid in which the station is located. Finally, similar to the process used for the measurements, the modelled concentrations of the stations were averaged to obtain a mean concentration for the Netherlands. This mean concentration was the input to the average risk approach.

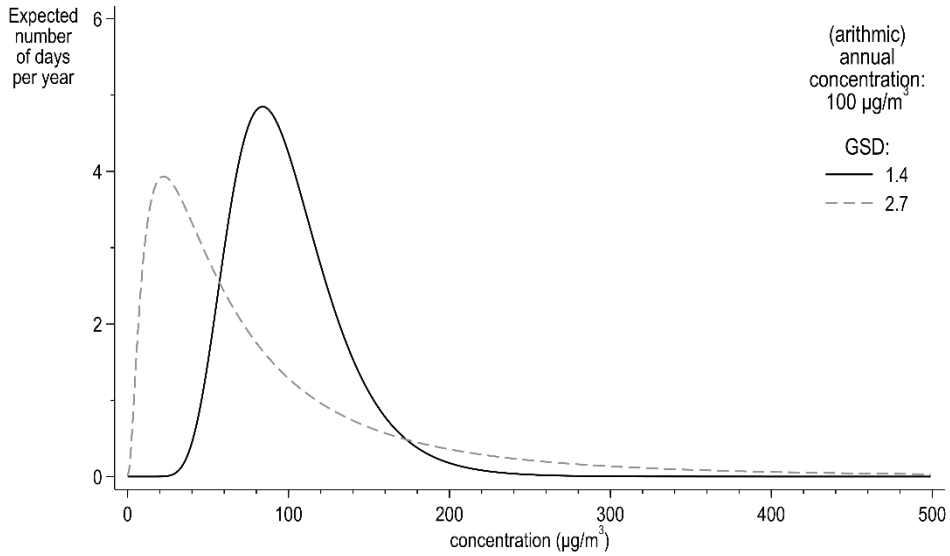
The GCN map for O_3 shows the 24-hour average concentration instead of the maximum 8-hour moving average concentration. Based on the ratio of 1.38 obtained from measurements at background stations in 2015-2019, we converted the 24-hour mean concentration to an estimated maximum 8-hour moving average concentration.

3.2.5 Simulation of distributions of daily concentrations

Series of daily concentrations of air pollution generally have a so-called lognormal distribution. The distribution of exposure is often skewed due to specific conditions (such as specific meteorological conditions or wild fires), which create long tails in the distribution. We have generated lognormal distributions with varying (arithmetic) annual mean concentrations and with varying geometric standard deviations (GSD). The GSD describes how much a series of daily concentrations are spread, and in case the exposure data is skewed, the GSD is a common descriptor to characterize the exposure distribution. The GSD is a multiplier and therefore dimensionless.

Figure 3.2 shows two simulated distributions of daily concentrations over a calendar year for a hypothetical air pollutant. Both distributions have the same arithmetic annual mean (100 µg/m^3) but different GSDs (1.4 and 2.7). The daily concentrations in this example have been generated with a resolution of 1 µg/m^3.

Figure 3.2 Examples of lognormal distributions of daily concentrations of a hypothetical air pollutant with the same (arithmetic) annual mean concentration but with varying geometric standard deviations (GSD).



The distribution with the highest variability is shown as dashed grey line. The most frequent daily concentration in this distribution with a GSD of 2.7 is 22 µg/m^3 and a (randomly chosen) concentration level of 300 µg/m^3 is exceeded about 20 times a year. The narrower distribution (black solid line) was simulated with a GSD of 1.4. The most frequent daily concentration is 84 µg/m^3 and the concentration level of 300 µg/m^3 is exceeded only once in about 10 years.

By generating exposure distributions with different GSDs for the same arithmetic mean, we can investigate how much the skewness of the distribution affects the bias of the average risk approach.

By generating different distributions with different arithmetic means, we can investigate how large the influence of the RR is on the bias of the average risk approach. According to equation [1] and equation [4], the size of the RR is partly determined by the (average) concentration.

3.2.6 Example from the Clean Air Agreement

To illustrate what the average risk approach could potentially mean for calculating the burden of acute effects in a future scenario, we clarify this in an example based on GCN maps generated for the second monitoring round of the Clean Air Agreement (Ruyssenaars, 2024).

The base year for the Clean Air Agreement is 2016. Four scenarios were calculated for the development of emissions in 2030 (Ruyssenaars, 2024). In this report we use the established policy as defined in the Climate and Energy Outlook. This is the 'KEV' scenario. The O_3 concentrations calculated for 2030 are only intended as input data for other air quality models and tools. It is not a true exploration of future concentrations.

3.3 Results

In section 3.3.1 we compare the PAFs based on series of daily measured concentrations at monitoring stations, using different calculation methods, and based on GCN maps.
It is conceivable that climate change will cause the weather to be different in the future than it is now, and that this will change the skewness of the exposure distributions. Also, air quality interventions can affect the distribution of pollutant levels. In section 3.3.2, we use simulated distributions to examine the effect of skewness on the application of the average risk approach. We also consider the role of the magnitude of the RR.
In section 3.3.3 we show the results of an application of the average risk approach in scenarios for the future, using data from the Clean Air Agreement.

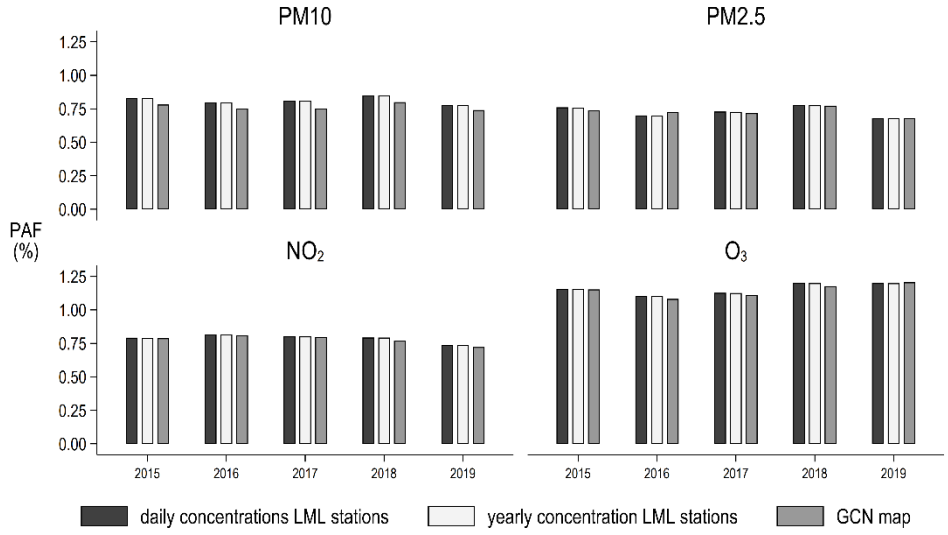
3.3.1 Comparison based on measurements in 2015-2019 and on GCN maps

Based on the daily measured concentrations at the LML background stations in 2015-2019, we calculated the daily attributable fraction and aggregated this for each calendar year. This was compared with the PAF based on an annual average of the measurements and the PAF based on extracted concentrations from the GCN maps. The mean of the five annual average concentrations and the range of the daily or annual concentrations are given in Table 3.2. The results of the PAFs are shown in Figure 3.3 for daily mortality.

Table 3.2 Mean of concentrations in the period 2015-2019 and the range based on daily or annual concentrations averaged over the LML background stations according to measurements and according to GCN maps. The range is given between brackets.

Component	Daily measurements	Annual average of daily measurements	Annual average GCN maps
PM10	18.6 (7-85)	18.6 (17.7-19.4)	17.5 (16.9-18.3)
PM2.5	10.8 (2-69)	10.8 (10.0-11.5)	10.7 (10.0-10.9)
NO_2	16.8 (4-52)	16.8 (15.8-17.4))	16.6 (15.4-17.3)
O_3	64.7 (3-201)	64.7 (61.7-67.1)	64.0 (60.4-67.4)

Figure 3.3 PAF (%) for mortality attributed to exposure to PM10, PM2.5, NO_2 and O_3 per calendar year based on daily measurements at LML background stations (in black), annual average of daily measurements (in white) and GCN maps (in grey) for 2016-2019.



When we compare the bars per component per calendar year, we see in Figure 3.3 that the PAFs based on daily or yearly concentrations and on GCN maps are almost identical.

The underestimation of PAFs based on measured annual concentrations compared to those based on measured daily concentrations is, in relative terms, less than 0.25% for all combinations of air pollutant and calendar year. The relative differences between PAFs based on measured annual concentrations and those based on concentrations from GCN maps are larger and vary between 4.7 and 7.1% for PM10, between -3.7 and 2.9% for PM2.5, between 0.4 and 2.9% for NO_2 and between -0.5 and 2.0% for O3. The change caused by the introduction of a concentration map instead of measurements (see Table 3.2 for the differences between concentrations) is larger than the change caused by the introduction of the average risk approach for the calculation of the PAF.

In Figure 3.4 we repeat the comparison for the combined exposure to PM10, NO_2 and O_3 per calendar year, using risk estimates from 2-pollutant models. We call the PAF indicative because there is no insight yet into the validity of the risk estimates from two pollutant models for the Dutch situation.
Again the differences are small. The underestimation of PAFs based on measured annual concentrations compared to those based on measured daily concentrations is less than 0.07% in Figure 3.4. The use of maps leads to an underestimation that varies between 1.5 and 3.2%.
The indicative PAF of the combined exposures using risk estimates from 2-pollutant models is about 2.1%; this corresponds to just over three thousand attributable deaths per year. If we had calculated the PAF

using risk estimates from single pollutant models, the PAF would have been about 2.7%, an overestimation of 30%.

Figure 3.4 Indicative PAF (%) for mortality attributed to the combined exposure to PM10, NO_2 and O_3 per calendar year using risk estimates from 2-pollutant models based on daily measurements at LML background stations (in black), on the annual average of daily measurements (in white) and on GCN maps (in grey) for 2016-2019.

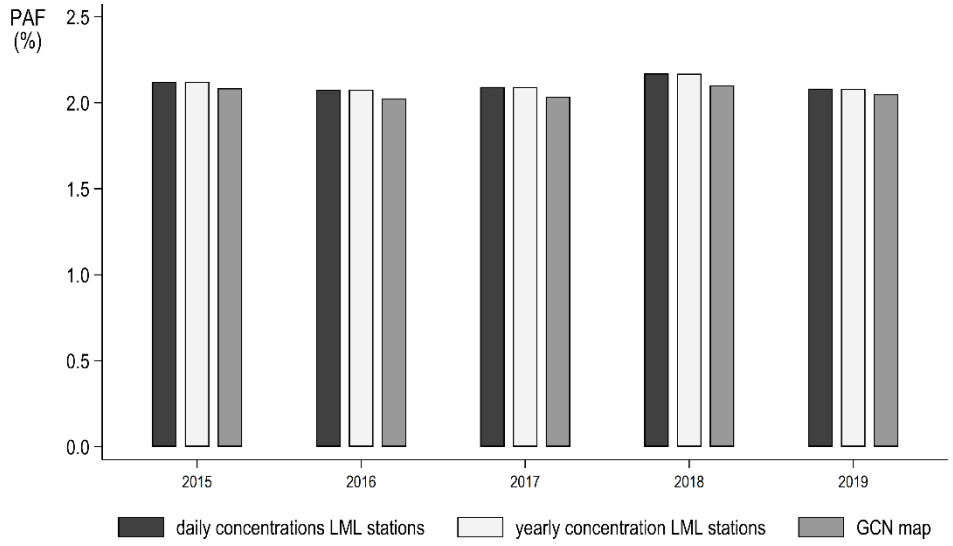


Figure 3.5 PAF (%) for emergency visits and hospital admissions due to asthma attributed to the exposure to PM10, PM2.5, NO_2 and O_3 per calendar year based on daily measurements at LML background stations, on the annual average of daily measurements and on GCN maps for 2016-2019.

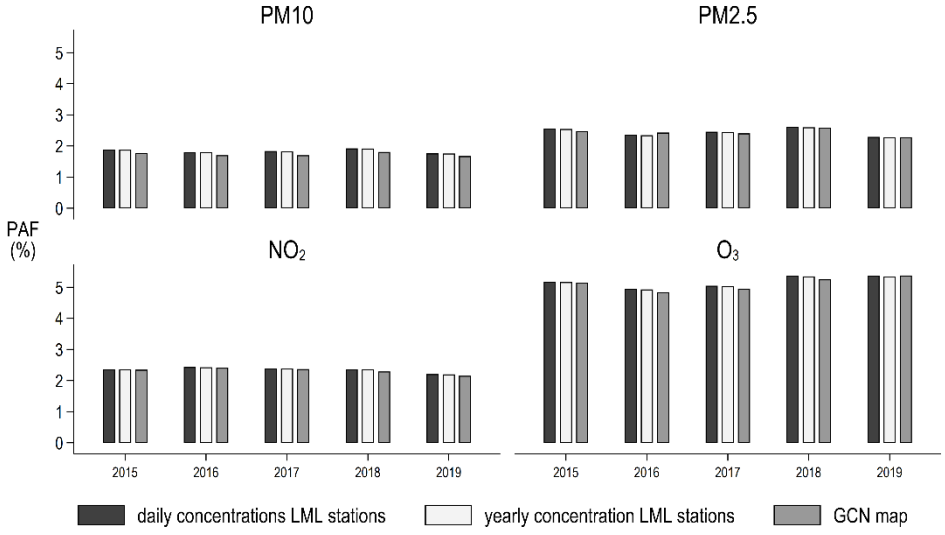
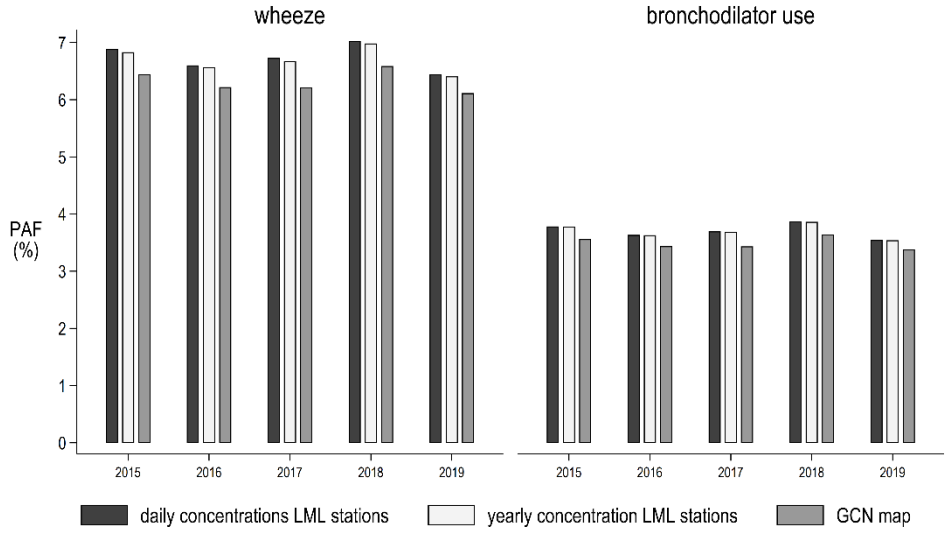


Figure 3.5 shows the results of the comparisons for emergency visits and hospital admissions for asthma.

The PAFs for emergency visits and hospital admissions are larger than those for mortality. Nevertheless, the underestimation due to the use of an annual average instead of daily concentrations from LML stations is less than 0.8%. The relative differences between PAFs based on measured annual concentrations and those based on concentrations from GCN maps are identical to those for mortality, as these differences are based on discrepancies in concentrations.
There are no risk estimates available for multi-pollutant models, so we did consider a comparison for the combined exposure.

The results for respiratory symptoms related to exposure to PM10 are shown in Figure 3.6.

Figure 3.6 PAF (%) for wheeze and bronchodilator use among COPD patients attributed to the exposure to PM10 per calendar year based on daily measurements at LML background stations, on the annual average of daily measurements and on GCN maps for 2016-2019.



Also for the respiratory symptoms, the results in Figure 3.6 indicate that, at current concentration levels, the average risk approach is a good alternative for calculations with daily concentrations.

3.3.2 *Comparison based on simulated exposure distributions*

We first investigated the historical distribution of the GSDs. The annual GSD for PM10 varied between 1.43 and 1.82; the average GSD was approx. 1.55. The annual average of the 24-hour average concentration in the period 1995-2019 could rise to 40 µg/m^3 for individual years. We then calculated the size of acute effects based on simulated daily exposure distributions with a GSD varying between 1.4 and 1.9 and with an annual mean concentration between 10 and 40 µg/m^3.

The difference between the PAF based on daily concentrations and on the average risk approach is shown for PM10 in Figure 3.7 for mortality and emergency visits and hospital admissions for asthma and in Figure 3.8 for respiratory symptoms.

Figure 3.7 Relative underestimation of PAF (%) for mortality and for emergency visits and hospital admissions attributed to PM10 exposure due to the average risk approach at different simulated concentrations and geometric standard deviations (GSDs).

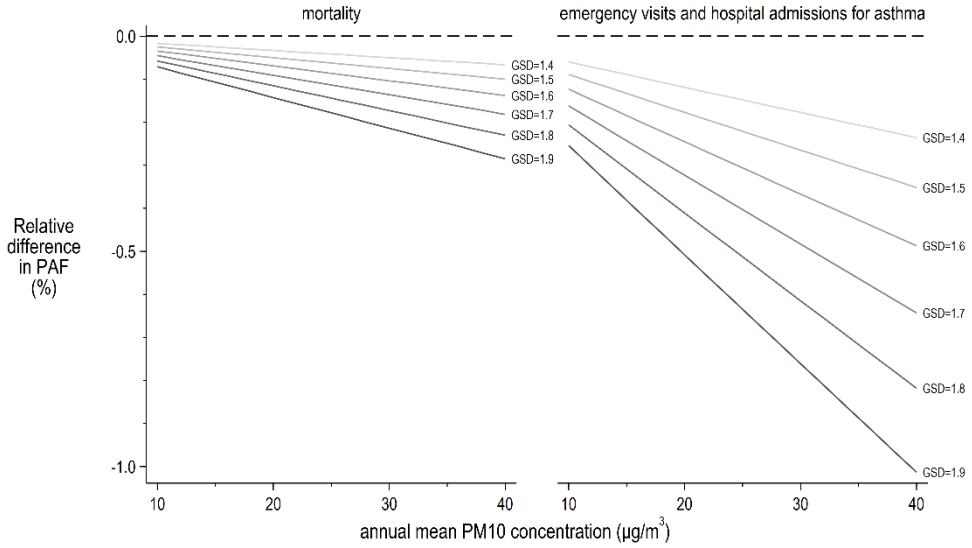
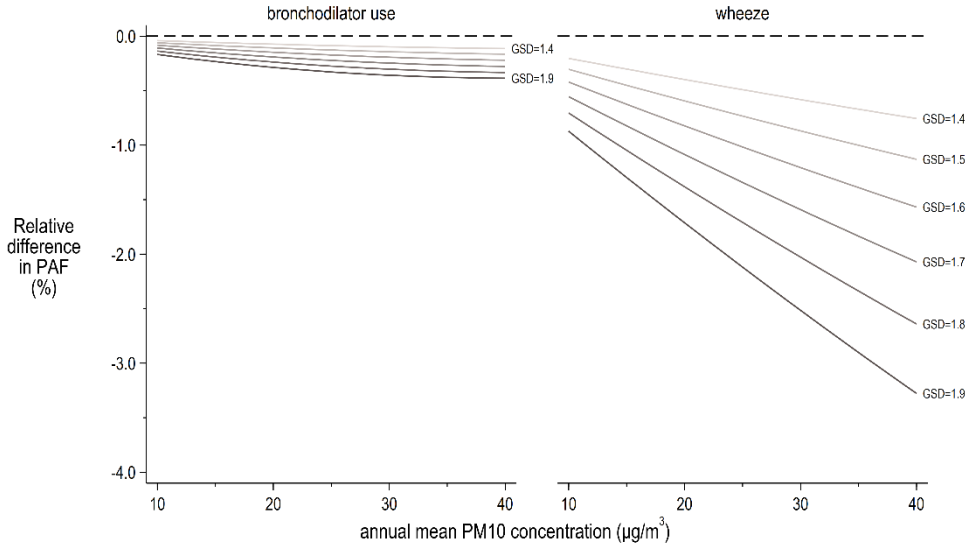


Figure 3.8 Relative underestimation of PAF (%) for the daily prevalence of bronchodilator use and of wheeze attributed to PM10 exposure due to the average risk approach at different simulated concentrations and geometric standard deviations (GSDs).



Underestimation by an average risk model is limited to a maximum of about 3% in extreme circumstances (high concentration and high variability). The underestimation increases with higher concentration (which is associated with an increasing RR) and with a higher geometric standard deviation. There is a difference in the degree to which the various health endpoints are underestimated by the average risk approach, which is related to the size of the risk estimate in the log-

linear model (Figure 3.8) or to the size of the risk estimate and the baseline prevalence in the case of a logistic model (Figure 3.9).

The results for mortality and for emergency visits and hospital admissions for asthma attributed to PM2.5, NO_2 and O_3 show the same pattern as in Figure 3.7. The results are included in appendix 2 and are summarised in Table 3.3. In the table, we have distinguished between realistic and less favourable assumptions. By the latter we mean simulated distributions with increased concentrations and increased GSDs.

Table 3.3 Summary of results for mortality and emergency visits and hospital admissions for asthma. Underestimation of the PAF in relative percentages by the average risk approach under realistic and under less favourable assumptions.

Pollutant	**Realistic assumptions**	**Less favourable assumptions**
PM10	<0.1-0.4%	0.1-1.0%
PM2.5	<0.1-1.0%	0.1-3.0%
NO_2	<0.1-0.5%	0.1-2.5%
O_3	<0.1-1.5%	0.1-4.1%

The results in Table 3.3 indicate that, under realistic assumptions about the development of the annual mean concentration and the variation of daily concentrations during the year, the underestimation due to the application of the average risk approach is for mortality and for emergency visits and hospital admissions for asthma limited to a maximum of 1.5%.

3.3.3 Clean Air Agreement

To illustrate how the average risk approach could be used in scenarios for the future, we carried out a case study using scenarios from the Clean Air Agreement.

Figure 3.9 shows the consequences of exposure to PM10, PM2.5, NO_2 and O_3, calculated in terms of the size of the acute effects in terms of the attributable number of deaths per year. The calculation is based on the MCC risk estimates from Table 2.4 and has been performed for two scenarios: the reference year 2016 and the future year 2030 with the so-called KEV (current policy) scenario. The figure also shows the effect of the combined exposure of PM10, NO_2 and O_3 on the size of the (expected) acute effects.

Figure 3.9 Attributed mortality per year in 2016 and 2030 by PM10, PM2.5, NO2 and O_3 according to the average risk approach. Example with data from the Clean Air Agreement.

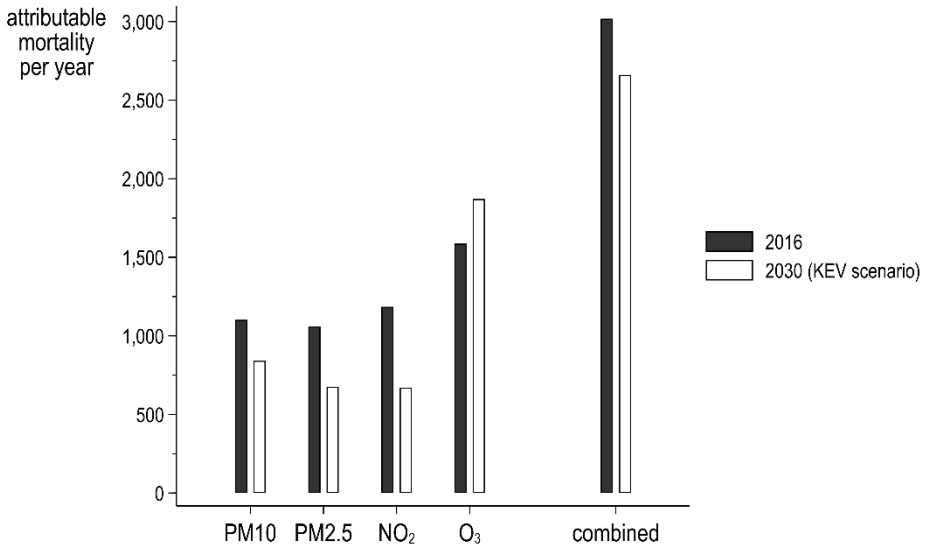


Figure 3.9 shows that the size of the acute effects attributed to PM10 and NO_2 is expected to decrease due to a reduction in concentrations, but that an expected increase in O_3 concentrations will lead to a rise in the risk of acute effects. The net result is a decrease in the size of the acute mortality attributable to air pollution. It should be noted that the calculations do not take into account population growth and possible changes in the vulnerability of the future population. In addition, the O_3 concentrations in 2030 are not based on a true exploration of future concentrations. It is also not yet clear whether the two pollutant estimates from the MCC that were used to calculate the combined exposure are valid for use in the Dutch situation.

3.4 Discussion and conclusions

3.4.1 Discussion

We have investigated whether it is possible to use an average risk approach to assess the burden of acute health effects due to short-term exposure. Our results indicate that this approach is effective. Although this approach leads to an underestimation of the burden of acute health effects, this underestimation is limited at current and lower concentrations and with assumptions about daily variation in air quality as has occurred in the past.

We examined the potential bias of the average risk approach by looking at the influence of the size of the RR and the skewness of the exposure distribution.
Underestimation increases with higher risk estimates in the log-linear model and with larger risk estimates and baseline prevalence in the logistic model. The magnitude of the underestimation is small (<1%) for the endpoints daily mortality, emergency visits and hospital admissions for asthma and bronchodilator use at current concentration levels and current variation in daily concentration levels; the underestimation is

slightly higher for wheeze. Under extreme circumstances (high concentration and high variability) the underestimation may increase up to 4%. If future trends in concentrations and/or variability are unfavourable, the selected health endpoints should be critically reviewed for their suitability for burden of disease calculations in situations where daily concentrations are not available.

We used the average risk approach in combination with large scale concentration maps (GCN) to predict future health effects. It was found that using concentrations from a GCN map instead of measured concentrations at background monitoring stations led to larger deviations in the PAF than was introduced by the use of the average risk approach. Therefore, given the uncertainties associated with predicting future concentrations and estimating the size of the associated health effects, the implications of using the average risk approach are limited.

The results show that the magnitude of acute effects is strongly correlated with annual average concentrations. The implication of these observations is that the magnitude of mortality attributed to exposure to long-term concentrations includes a large proportion of daily deaths due to daily concentrations. It is therefore incorrect to add the number of deaths attributed to short-term exposure to the number of deaths attributed to long-term exposure.

The results on emergency visits and hospital admissions for asthma, as well as the exacerbation of respiratory symptoms, show that episodes of increased air pollution can lead to a wide range of health problems. It is desirable to verify the E-R relationships for hospital admissions based on international studies for the Dutch situation in order to get a true picture of the effects of air pollution in the Netherlands. In addition, it is useful to conduct research with patient groups to get a picture of the extent of their daily complaints that can be attributed to air pollution.

We used the (linear) risk estimates for PM, NO_2 and O_3 obtained from (loglinear) Poisson models in MCC studies (Liu et al., 2019; Meng et al., 2021; Vicedo-Cabrera et al., 2020) to estimate the burden of attributable mortality in the Netherlands, since our estimates obtained for the period 1995-2019 are in the same order, and MCC is the only (large) sources for estimates from two-pollutant models (Liu et al., 2019; Meng et al., 2021; Vicedo-Cabrera et al., 2020). Meng et al. (Meng et al., 2021) concluded that the E-R relation for NO_2 is almost linear, and Vicedo-Cabrera et al. (Vicedo-Cabrera et al., 2020) indicated that there is no evidence of a non-linear relation for O_3. For PM10 and PM2.5, Lui et al. (Liu et al., 2019) reported that the slopes of the E-R curves were steeper at concentrations below 40 µg/m^3 for PM10 and below 20 µg/m^3 for PM2.5. The slopes seemed to flatten at higher concentration levels: the curves have a concave shape.
If the RR function is concave, the average risk approach will overestimate the PAF. As the majority of current daily concentrations of PM10 and PM2.5 are below 40 and 20 µg/m^3 respectively, and levels of these air pollutants are expected to decrease, we assume that the overestimation will be limited. Given the (almost) linear E-R relations for NO_2 and O_3, we did not find it necessary for these components to assess

the consequences of the shape of the E-R relation for the application of the average risk approach.

For emergency visits and hospital admissions for asthma related to PM, no information on the shape of the E-R relation is available. The shape of the E-R relations for O_3 and NO_2 is described qualitatively in the publications by Zheng (Zheng et al., 2015; Zheng et al., 2021). For O_3, the shape was described in six publications, three of which discussed a non-linear relationship. For NO_2 this was the case in three out of three papers. If quantitative information on the shape of the E-R relation for this health endpoint becomes available in the future, and if it is found to be significantly non-linear, it is recommended that the average risk approach be re-evaluated. The influence of the shape of the curve can be determined by simulation. See Ruan et al. (2021) for details (Ruan et al., 2021).

Using data from the Clean Air Agreement monitoring report as an example, we have shown that the average risk approach can be used for future scenarios. It should be noted that modelling of future O_3 concentrations is not (yet) fully developed for this type of monitoring. Furthermore, the risks of long-term exposure to PM and NO_2 are combined in the Clean Air Agreement. In principle, this could also be done for the acute effects of air pollution. For this, it would be necessary to test whether, for example, the risk estimates from multi-pollutant models reported by the MCC are valid for the Dutch situation.

3.4.2 Conclusions

The average risk approach is well suited for estimating the burden of disease due to short-term exposure to air pollution.

The extent of underestimation by the average risk approach is limited at current and lower concentrations and with assumptions about daily variations in air quality as in the past.

The burden of health effects due to short-term exposure in future scenarios can be calculated on the basis of large-scale annual average concentration maps. The modelling of future O_3 concentrations is a point of attention.

4 Part 3 High-risk groups for health effects due to short-term exposure to air pollution: a pilot study

4.1 Introduction

In the previous chapters we looked at the full Dutch population in terms of health risks due to variations in daily concentrations of air pollutants and how we can easily determine the magnitude of these risks in (future) scenarios. In this chapter, we focus on identifying people who are at additional risk of acute health effects when concentrations increase, the so-called high-risk groups.

4.1.1 High risk groups

Following an earlier recommendation of the Health Council of the Netherlands on high-risk groups (Gezondheidsraad, 2011), there are two possible approaches to defining high-risk groups: based on air pollutants with an acute health risk, in this case, or based on a disease or disorder. A high-risk group may therefore consist of:

- people with a particular characteristic that adversely affects exposure to or sensitivity to an air pollutant (or both)
- people with a particular characteristic that increases the likelihood of the disease or disorder.

A high risk group is a relative term. It refers to a subpopulation that is more likely to be exposed to elevated concentrations of an air pollutant or more likely to develop an acute response (mortality, hospital admission, exacerbation of respiratory symptoms) due to short-term exposure than the rest of the population.

Many factors can influence the risk of an acute effect:

- personal characteristics, including gender, age, genetic characteristics, health status (fitness, pre-existing diseases)
- lifestyle characteristics
- characteristics of the physical and social environment.

It is important to understand the factors that modify the acute health risk of short-term exposure to air pollutants so that effective adaptation and/or mitigation measures can be taken and early warning systems, such as the LKI (Dutch Air Quality Index)(Dusseldorp, 2015), or sources of information on the spatial distribution of air pollution risks, such as the Atlas Leefomgeving (www.atlasleefomgeving.nl), can be improved.

4.1.2 Objectives

A pilot study has been undertaken to assess the epidemiological research needed to identify high-risk groups and locations for acute health risks from short-term exposure to air pollutants. The research questions are:

- Which individual and neighbourhood factors in the Netherlands contribute to the risk of acute health problems due to short-term exposure?

- Is it possible to quantify these additional risks so that communication about the acute effects of air pollution can be better tailored to high-risk groups and/or high-risk locations?

We are particularly interested in effect modification. Effect modification means that the shape of the relationship between air pollution and health risk is not the same for every group; for example, the relationship may be steeper for older people than for young people. Understanding effect modification helps to identify which groups are most affected by a risk factor.

4.2 Methods

A brief literature review was conducted to identify potential effect modifying factors.
It was considered appropriate to test whether a pilot study could be conducted with a relatively simple study design with one air pollutant and in a limited timeframe as a 'proof of concept' for effect modification research in relation to short-term exposure to air pollutants.

4.2.1 Exploratory epidemiological study

We explored the possibility of quantifying effect-modifying factors using daily mortality databases, spatially or individual linked to daily air pollution databases and relevant (individual) demographic, health, physical environment and neighbourhood datasets.

We used a dataset that had previously been compiled for a study of the effects of heat. This means that the research period was limited to the five hottest months of the year (May-September). We also chose to focus on O_3 because concentrations are higher in the summer.

To study which factors modify a person's risk due to a time-varying exposure, it is possible to restrict the statistical analysis to persons who died (cases). The basic idea of this case-only design is that if a time-invariant characteristic (like diabetes, sex) is more often present in cases on days with high O_3 concentrations, than in cases on days with low O_3 levels, then this is evidence that the specific factor is an potential effect modifier and affects the associations between exposure (O_3) and outcome (mortality)(Armstrong, 2003). Given that in a case-only design the prevalence of a time-invariant condition on being a case—rather than the number of the cases— is modelled, time-varying factors that predict the number of cases (like weather and season) are considered irrelevant and were not included in the statistical analysis (Medina-Ramon & Schwartz, 2008).

We used existing registrations available as microdata sets from Statistics Netherlands (CBS). The CBS combines data from the municipal key register to form a longitudinal file for all persons (de Bruin et al., 2004). Changes in demographic characteristics (e.g. births, deaths, address, marital status, emigration) are continuously updated by adding additional information on the nature and date of the change. Individual records can be linked via a unique personal identification number and to the home address in relation to a unique address object identification number. Statistics Netherlands has secure computing facilities available

for statistical analysis (with the permission of the CBS and the owners of the records).

The files can be enriched with information from other central data sources of the CBS. Cause of death statistics were used as a proxy for underlying disease. Data were provided by the CBS based on municipal population registers at the individual level (Harteloh et al., 2010). We focused on causes of death due to cardiovascular, respiratory or neurodegenerative diseases. We enriched individual demographic information with individual standardised disposable household income, adjusted for individual household size and composition, and household financial prosperity, based on both standardised income and assets.

Based on the address, we linked the socio-economic status of the neighbourhood and the degree of urbanisation to the dataset. The CBS has collated figures on financial wealth, educational attainment and recent employment history and calculated a combined score for each neighbourhood based on the data for each household. The score shows at a glance how the neighbourhood compares with other neighbourhoods on these three elements of socio-economic status. The degree of urbanisation is based on the average density of addresses within a 1 km radius, divided into five categories: very strongly urbanised (≥2500 addresses per km^2), highly urbanised (1500-2499 addresses per km^2), moderately urbanised (1000-1499 addresses per km^2), low urbanised (500-999 addresses per km^2) to non-urbanised (<500 addresses per km^2).

Daily O_3 concentrations were obtained from urban and rural background monitoring stations in the LML and uploaded to the secure computing facilities of the CBS. The same data set was used as in the previous chapters. The daily concentrations per part of the country (northern, eastern, western and southern Netherlands) were linked to the addresses of the deceased.
We used the average maximum 8-hour O_3 concentration for the day of death and the day before as a first indicator of short-term exposure. We then defined days with high O_3 concentrations based on the 99th percentile of concentrations among the deceased.

The cohort was followed from 1 January 2013 to 31 December 2019. As the CBS introduced an automated coding system for cause-of-death statistics in 2013 (Harteloh, 2020), which led to a shift in the occurrence of causes of death, we did not use statistics before 2013. Only persons aged 60 years or older in the calendar year of death and living at home were included in the statistical analyses.

4.3 Results

4.3.1 Effect modifiers in the literature

Table 4.1 provides an overview of individual and community characteristics that have been identified as potentially contributing to the vulnerability of high-risk groups to short-term exposure to O_3 exposure in relation to mortality and hospital admissions (Bell et al., 2014).

Table 4.1 Evidence on characteristics that may contribute to the vulnerability to short-term exposure to O_3 in relation to mortality and hospital admissions (adapted from:(Bell et al., 2014)).

Characteristic	# of studies	Evidence of association	Direction of risk
Gender	36	limited/suggestive	higher for women
Age	89	strong	higher for elderly
Ethnicity	8	weak	higher under minority groups
Education	10	weak	higher with lower educational level
Income	9	no	-
Occupation/ employment	5	strong	higher with lower employment status
Poverty	8	weak	higher in high-poverty areas
Air conditioning	5	weak	higher with lower AC prevalence

Except for strong evidence of effect modification by age and employment status, the tables show weak, limited or suggestive evidence for other individual or community characteristics. However, the number of studies on potential effect modifiers was limited, except for those on age and gender.

4.3.2 Exploratory epidemiological study

The epidemiological study was conducted on a population of deceased persons who died during the five hottest months (May-September) in the period 2013-2019, were aged 60 years or older in the calendar year of death and lived at home. Almost 294,000 people were included. A concentration of 156 µg/m^3 was found to be the one at or above which 1% of the population died.
For a selection of individual, household and neighbourhood characteristics, we examined whether these were more common among those who died on days with O_3 concentrations of 156 µg/m^3 or more compared to those who died on days below 156 µg/m^3.

Figure 4.1 shows the potential effect modification of age. Eight age groups are shown on the vertical axis. A percentage is shown next to the categories. This is the percentage of the prevalence of the group in the total population of deceased. The age group 60-64 is the reference group; 7.5% of the deceased belonged to this age group. The reference group can be recognised in Figure 4.1 as this group has a (modifying) effect of 0% (shown on the horizontal axis) and its 95% confidence interval is missing.

Figure 4.1 The size of the effect modification in relative percentage and its 95% confidence interval by age. The risk in the 60-64 age group is the reference (no effect modification: 0%).

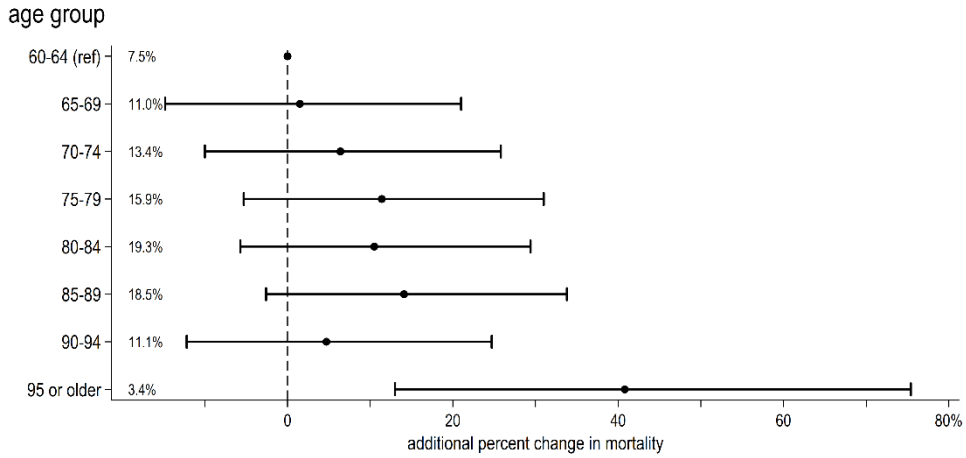
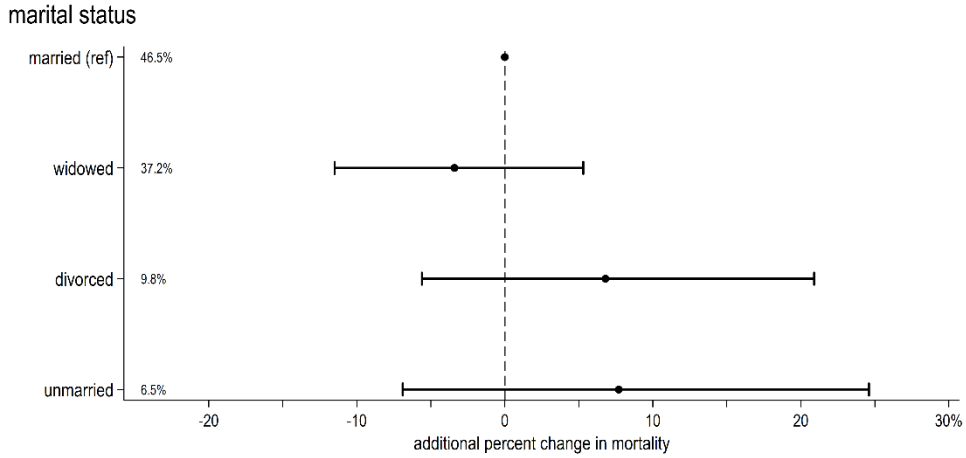


Figure 4.1 shows that in people aged 95 and higher, the association between short term exposure to high ozone levels and mortality is about 40% higher compared to the association for people in the reference group (60-64 years old). This result suggests that being 95 years or older, on average 3.4% of the deceased, is an additional risk in the relation between short-term O_3 exposure and acute mortality.

Similarly, the results for marital status are presented in Figure 4.2.

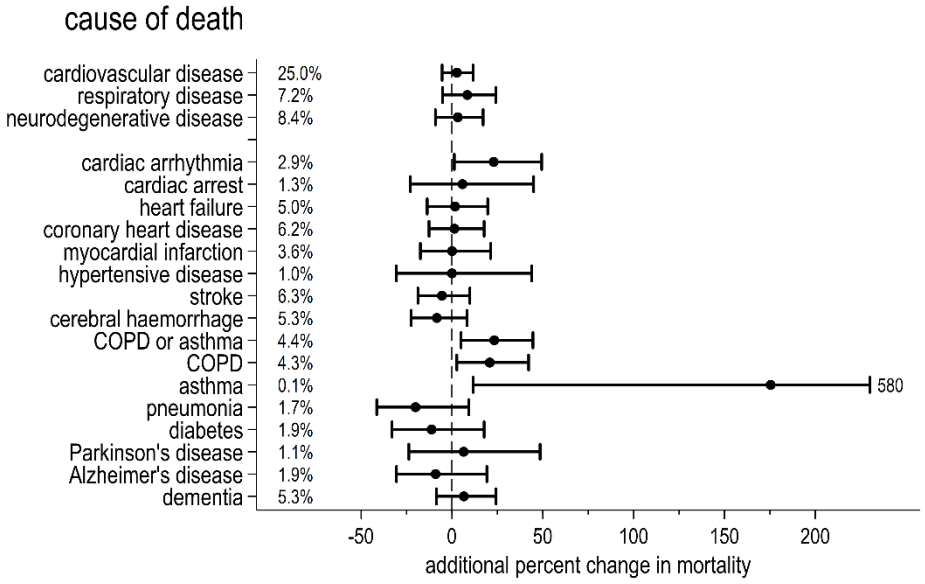
Figure 4.2 The size of effect modification in relative percentage and its 95% confidence interval by marital status. Married people are the reference (no effect modification: 0%).



Although the results in Figure 4.2 suggest that being divorced or unmarried is associated with a 5-10% higher risk of mortality as result of short-term exposure to O_3 levels compared with being married, there is no evidence to suggest that marital status is an effect modifier, as all 95% confidence intervals include an effect of 0%.

To see if health status is an effect modifying factor, we have conveniently used cause of death as a proxy for the only underlying condition that the deceased had prior to their death (Figure 4.3). The layout of Figure 4.3 differs from the previous two in that the reference group is not shown. In this case, the cause of death in question is compared with all other causes of death.

Figure 4.3 The size of the effect modification in relative percentage and its 95% confidence interval by cause of death as a proxy for underlying disease. For each of the causes, the risk among people who died from another cause is the reference (not shown).



The first three lines in Figure 4.3 shows that people with cardiovascular disease, respiratory disease or neurodegenerative disease are generally not at increased risk on days with elevated O_3 levels.
When we zoom in on 16 specific causes of death, we see that having cardiac arrhythmia, asthma or COPD is associated with an increased risk. Having asthma more than doubles the risk of acute mortality from O_3 exposure, as shown in Figure 4.3. However, it should be noted that the magnitude of this additional risk is subject to much uncertainty due to the relatively small number of people for whom asthma is diagnosed as the cause of death.

We have given three examples of individual characteristics as potential effect-modifying modifiers. Using the CBS data, it is also possible to look at household characteristics. Figure 4.4 shows the results for household income. Figure 4.5 looks at household wealth.

Figure 4.4 The size of effect modification in relative percentage and its 95% confidence interval by percentiles of household income. The reference group is made up of deceased persons with a household income between the 40th and 60th percentile (no effect modification: 0%).

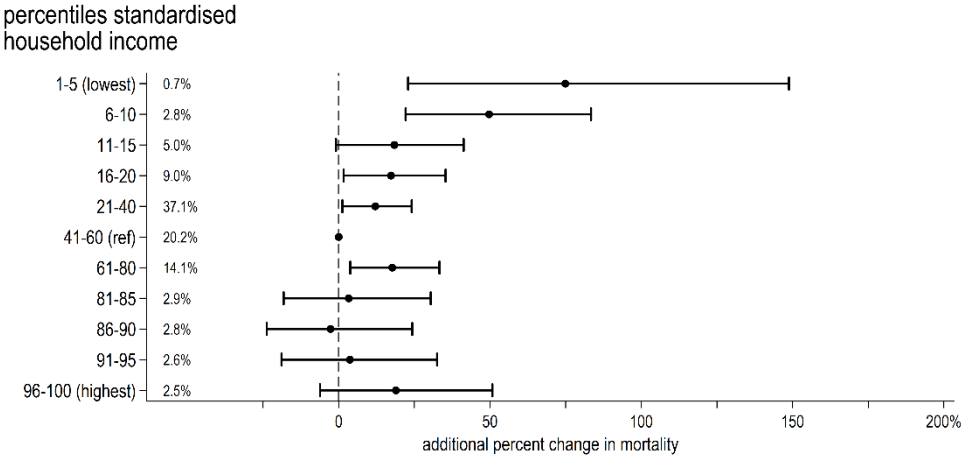
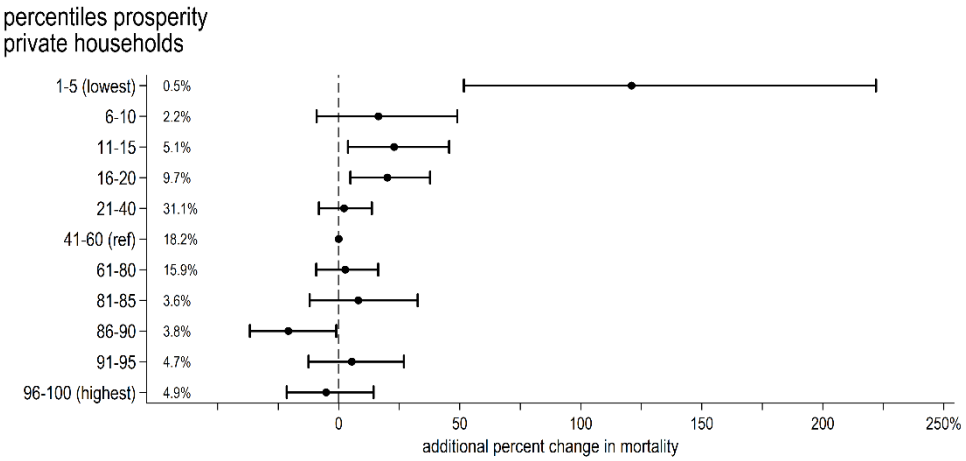


Figure 4.5 The size of effect modification in relative percentage and its 95% confidence interval by percentile of prosperity private households.. The reference group is made up of deceased persons with a household income between the 40th and 60th percentile (no effect modification: 0%).



The results in Figure 4.4 and Figure 4.5 indicate that lower household income or lower wealth is an effect-modifying factor. The risk of belonging to the lowest percentiles (1-5) of all households in the Netherlands increases the risk by about 125%, although again it should be pointed out that the size of this extra risk is subject to uncertainty due to the relatively small number of elderly people in these lowest percentiles (<1%).

Finally, two examples of potential effect modifiers at the neighbourhood level, the socio-economic status of the neighbourhood and the degree of urbanisation, are shown in Figures 4.6 and 4.7.

Figure 4.6 The size of effect modification in relative percentage and its 95% confidence interval by categories of socio-economic status of the neighbourhood. The reference group is made up of deceased persons with a household income between the 40th and 60th percentile (no effect modification: 0%).

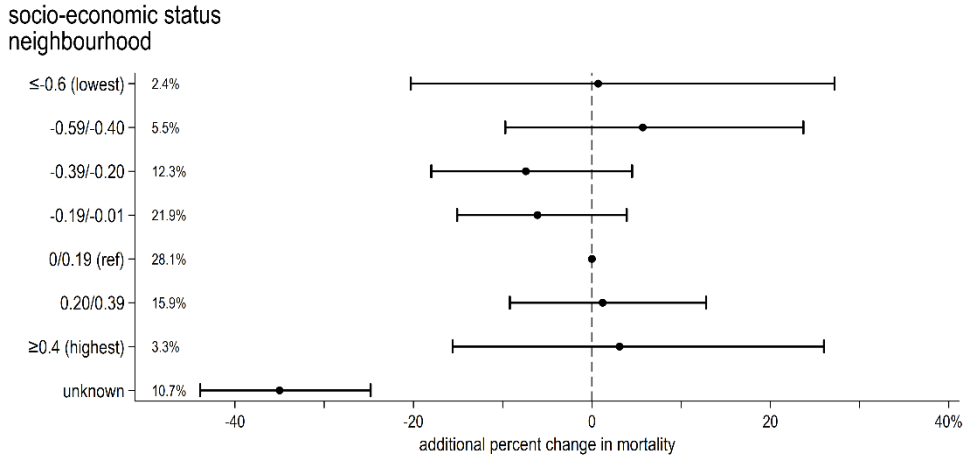
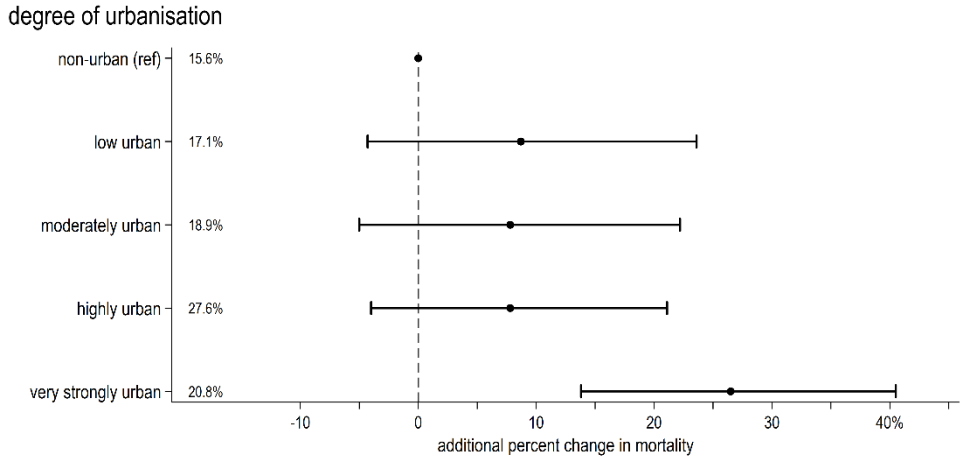


Figure 4.7 The size of effect modification in relative percentage and its 95% confidence interval by categories of the degree of urbanisation of the neighbourhood. The reference group is made up of deceased persons with a household income between the 40th and 60th percentile (no effect modification: 0%).



The potential modifying effect the by the socio-economic status of the neighbourhood is unclear (Figure 4.6). Among people for whom the socio-economic status of the neighbourhood is known, there is no effect modification by this factor. It is striking, and not immediately explainable, that when the status is unknown, a protective effect is revealed by the statistical analyses.
Living in a very strongly urbanised neighbourhood is an effect modifying factor, as shown in Figure 4.7.

4.4 Discussion and conclusions

4.4.1 Discussion

When developing air pollution prevention policy, it makes sense to focus more consistently and systematically on groups of people who are at a higher than average risk of experiencing acute health effects.

In 2018, the Health Council of the Netherlands stated in its advice 'Health benefits through cleaner air' (in Dutch: Gezondheidswinst door schonere Lucht) that, in addition to general measures to protect everyone in the Netherlands, further health benefits can be achieved by taking into account high-risk groups. These are people who are exposed to high levels of air pollution for long periods of time, as well as people who are particularly sensitive to air pollution because of their age (children and the elderly) or illness (Gezondsheidsraad, 2018).
To protect highly exposed groups, the Committee recommends additional measures around 'hot spots'. To specifically protect highly sensitive groups, the Commission advocates a 'sensitive destination policy': no facilities for children and the elderly near a hotspot. To provide additional protection for sensitive groups, the Committee advocates more active dissemination of specific behavioural advice, such as avoiding strenuous exercise or staying indoors during periods of O_3 smog in the afternoon.

In this chapter we have explored whether it would be possible to extend the Health Council's recommendations on highly sensitive groups in the future. We did this by carrying out a pilot study that looked not only at individual-level factors (such as age and underlying diseases), but also at potential effect-modifying factors related to household or neighbourhood characteristics.
The underlying idea is that it should be possible to use a combination of a set of relevant effect-modifying factors at the individual, household and neighbourhood level and detailed spatial information on short-term exposure to identify who high-risk individuals are and to 'map' where high-risk groups live. In this way, hotspots could be identified for high-risk groups for short-term exposure to air pollutants, so that additional effective measures can be taken. This small-area assessment of high-risk groups has recently been successfully applied for daily temperature, e.g. in England and Wales for lower-layer super output areas (about 1000-3000 inhabitants) (Gasparrini et al., 2022) and in Norway at the municipality level (Vazquez Fernandez et al., 2025).
Also, the dissemination of specific behavioural advice can be improved with new information on the factors that contribute to high risk groups.

The exploratory analyses reveal indications of effect modification of the risk of short-term exposure to O_3 due to age, underlying illnesses (asthma, COPD, cardiac arrhythmia), household income and prosperity, and degree of urbanisation.
The exploratory epidemiological analysis shows in general that it is possible to gain insight into effect modifying factors for O_3-related mortality based on existing data. A larger follow-up study could answer the question of which demographic and socioeconomic factors, pre-existing health conditions, housing and neighbourhood characteristics increase the risk of mortality, hospitalisation or GP visits on days with

elevated PM, NO_2 and/or O_3 concentrations. For factors other than age, the evidence for effect modification is still limited.

We chose to use a relatively simple method to detect potential effect modification in this pilot study. We wanted to demonstrate that this type of research is possible and to identify the obstacles we would face if we were to continue and expand this research. We have identified two key improvements.
First, the spatial resolution of short-term exposure can be improved. We now assign separate daily O_3 concentrations to addresses in the four regions of the country. In principle, it is possible to use the RIO model that generates hourly air pollutant concentrations on a grid of 1 km by 1 km (Mooibroek, 2014). This would allow us to take much better account of spatial differences in air quality and also brings us a significant step closer to identifying high-risk groups at high spatial resolution, such as neighbourhoods or districts.
In addition, a better statistical method can be used. We have now compared the risks on the 1% of days with high O_3 concentrations with the risks on the other 99% of days. We only make limited use of the differences in O_3 concentrations between days (and between locations). In the event of a possible follow-up, we would like to use the recently developed case time series design (Gasparrini, 2021). The case time series design combines the best of two worlds: retaining the individual-level setting of the case-only design used in this chapter, and the temporal structure and modelling flexibility of the time series design used in Chapter 2. We are currently investigating the possibilities of this case time series design and the level of aggregation at which it can be applied in a temperature-related study.

4.4.2 Conclusions

- Knowledge of the factors that contribute to the risk of acute health effects due to short-term exposure to air pollution is still limited.
- This pilot study shows that existing data can be used to gain insight into effect-modifying factors at the individual, household and neighbourhood levels.
- This pilot study has identified a number of ways to improve the conduct of research in a possible follow-up study.
- With these improvements, it will be possible in the future to quantify and spatially represent the risks of effect-modifying factors. This will allow communication of the risks of short-term exposure to be better tailored to existing high-risk groups and/or high-risk environments.

5 General conclusion and recommendations

The goal of this report was to study risk of variations in daily concentrations of air pollution on mortality and health. The report consists of three parts.

The main aim of part 1 (chapter 2) was to evaluate whether the Dutch air quality policy is effective to reduce the health risks due to short-term exposure and if the emission reducing measures target the right components by studying trends in associations between air pollution and daily mortality. Levels of PM10, PM2.5 and NO_2 decreased considerably between the period of 1995 and 2019 in the Netherlands, while O_3 levels increased slightly. There was no evidence that the toxicity of air pollution increased over time; we found no indications for an increased trend (per fixed increment of 10 ug/m^3) in the risks estimates of the association between air pollution and daily mortality in the Netherlands during the study period 1995-2019. For NO_2, effect estimates appeared to decline. The reason for this remains unclear. As the chemical composition of NO_2 does not change, this finding could indicate a reduction on other combustion-related pollutants, such as soot or UFPs. The total number of deaths attributable to air pollution decreased over the same period. This indicates that Dutch air quality policy have been effective over the past 25 years, except for O_3. Nevertheless, the findings still indicate an increased risk from short-term exposure. It is expected that a further reduction in concentrations will lead to a further decrease in the attributable risks and the size of attributable daily mortality. Additionally, these results suggest that ozone is playing an increasingly significant role. It is, therefore, becoming more relevant to examine the effects of ozone.

In part 2 (chapter 3) we examined whether the burden of acute health effects caused by air pollution can also be modelled in a simple way, by using the so-called ‘average-risk approach’. To model the extent of acute health effects in a calendar year, daily concentrations of particulate matter, NO_2, and ozone are required. To estimate how the disease burden of air pollution will develop in the future or to calculate the effect of potential regulations and other interventions (scenarios), it is desirable to have a simpler method available, because modelling daily concentrations based on emissions and weather requires extra effort compared to calculating annual average concentrations. Our results indicate that the average risk approach is well suited for estimating the burden of future acute effects of air pollution, for example to calculate the burden for different scenarios as in the Clean Air Agreement (in Dutch: het Schone Lucht Akkoord (‘SLA’)). The modelling of future ozone concentrations is a point of attention. Furthermore, the risks of long-term exposure to PM and NO_2 are combined in the Clean Air Agreement. It would be necessary to test whether this also could be done for the acute effects of short-term exposure to air pollution, by evaluating whether risk estimates from multi-pollutant models are valid and can be applied to the Dutch situation.

In part 3 (chapter 4), a pilot study has been undertaken to assess the epidemiological research needed to identify high-risk groups and locations for acute health risks from short-term exposure to air pollutants. When developing prevention policy for air pollution, it makes sense to focus more consistently and systematically on groups of people who run a higher than average risk of acute health effects. The exploratory analysis indicates that existing data can provide insights into effect-modifying factors. Before a more extensive follow-up study can be carried out, further development of the statistical method is necessary.

Proposed recommendations for future (research) activities are:

- the extent of health effects from exposure to short-term concentrations of PM10 and NO_2 has decreased over the years, and ozone is playing an increasingly significant role. It is, therefore, becoming more and more relevant to examine the health effects of ozone
- The application of summed risk estimates for air pollutants from multiple single-pollutant models may lead in health impact assessments to an overestimation of the disease burden, since short-term exposure to air pollutants is correlated. We therefore recommend to assess the health effect of exposure to multiple exposures in one model. In addition, a more recent proposed approach, by using the combined O_3 and NO_2 oxidative capacity (O_x) can be used. This information helps policy makers to take better informed (cost-)effective measures.
- Climate change modifies weather patterns, which affects exposure to environmental health risk factors, including outdoor air pollutants, extreme temperatures and aeroallergens, such as pollen and these factors might have synergistic effects on health outcomes. Therefore, it is necessary to investigate how combined environmental exposures interact and their short-term exposures have impact on human health.
- focus more consistently and systematically on groups of people who have a higher than average risk of acute health effects. This will allow improved future projections and communication of the risks of short-term exposure to be better tailored to existing high-risk groups and/or high-risk environments, for instance in relation to 'early warning' systems such as the ‘LKI’ or smog alerts.
- Further development of the statistical method to project the acute health risks of daily concentrations to a small-area level, taking into account demographic, socioeconomic, housing, neighborhood, and area characteristics, to facilitate discussions with local and regional stakeholders about the effects of air pollution.
- In addition to effects on mortality, conduct additional analyses of air pollution on morbidity data such as hospital admissions or exacerbation of respiratory complaints in patient groups
- regular (5 years interval) re-analyses of trends in associations to evaluate potential changes in associations between air pollution and health and potential changes of the air pollution mixture, but also in order to use the state-of-art-estimates by including the most recent literature and analyses techniques.

- annually update of a quantification of the acute health effects attributable to short term air pollution, as was done up to 2014 in the Environmental Data Compendium.

Acknowledgements

We thank the Dutch Working Group on Clinical Virology from the Dutch Society for Clinical Microbiology (NVMM) and all participating laboratories for providing the virological data from the weekly Sentinel Surveillance system and Letty de Weger from Leiden University Medical Center and Mieke Koenders from Elkerliek Hospital Helmond for providing the pollen data.

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Appendix 1

Table A1 Selected air pollutants that were measured per monitoring site.

Site ID	Site name	Start date*	End date*	PM10	PM2.5	NO_2	O_3
Rural Background							
107	Posterholt	1-1-1995	31-12-2019	☐	☐	☑	☑
131	Vredepeel	1-1-1995	31-12-2019	☑	☑	☑	☑
133	Wijnandsrade	1-1-1995	31-12-2019	☑	☐	☑	☑
227	Budel	1-1-1995	31-12-2019	☐	☐	☑	☑
230	Biest-Houtakker	1-1-1995	31-12-2019	☑	☑	☑	☑
232	Volkel	1-1-1995	31-3-2002	☐	☐	☑	☑
235	Huijbergen	1-1-1995	31-12-2019	☑	☐	☑	☑
243	De Rips-Blaarpeelweg	3-8-2007	17-1-2016	☑	☐	☐	☐
244	De Rips-Klotterpeellaan	10-8-2007	18-1-2016	☑	☐	☐	☐
245	Moerdijk	21-7-2007	19-3-2013	☑	☐	☑	☐
246	Fijnaart	6-10-2007	31-12-2019	☑	☑	☑	☐
301	Zierikzee	1-1-1995	31-12-2019	☐	☐	☑	☑
312	Axel	1-8-2007	27-2-2013	☑	☐	☐	☐
318	Philipine	1-1-1995	31-12-2019	☑	☐	☑	☑
319	Nieuwdorp	1-10-2009	1-12-2014	☑	☐	☐	☐
411	Schipluiden	1-1-1995	1-1-2013	☐	☐	☑	☑
437	Westmaas	1-1-1995	31-12-2019	☑	☐	☑	☑
444	De Zilk	1-1-1995	31-12-2019	☑	☑	☑	☑
507	Kwadijk-Westerweg	1-1-1995	31-12-1996	☐	☐	☑	☑
538	Wieringerwerf	1-1-1995	31-12-2019	☑	☑	☑	☑
620	Cabauw	1-1-1995	31-12-2011	☐	☑	☑	☑
617	Biddinghuizen - Kuilweg	11-6-2015	31-12-2019	☑	☐	☑	☑
627	Bilthoven	20-8-2009	31-12-2010	☐	☑	☐	☐
631	Biddinghuizen - Hoekwantweg	1-1-1995	10-4-2017	☑	☐	☑	☑
633	Zegveld	1-1-1995	31-12-2019	☑	☐	☑	☑
644	Cabauw	31-3-2011	31-12-2019	☑	☑	☑	☑
722	Eibergen	1-1-1995	31-12-2019	☑	☐	☑	☑
724	Wageningen	1-1-1995	22-4-2002	☑	☐	☑	☑
733	Loenen	1-1-1995	22-4-2002	☐	☐	☑	☑
738	Wekerom	27-4-2002	31-12-2019	☑	☑	☑	☑
743	Kootwijkerbroek	7-11-2008	8-7-2013	☑	☐	☐	☐
744	Barneveld	11-12-2008	8-2-2012	☑	☐	☐	☐
807	Hellendoorn	1-1-1995	31-12-2019	☑	☑	☑	☑

Site ID	Site name	Start date*	End date*	PM10	PM2.5	NO_2	O_3
818	Barsbeek	1-1-1995	31-12-2019	☑	☐	☑	☑
913	Sappemeer	1-1-1995	31-3-2002	☐	☐	☑	☑
918	Balk	1-1-1995	31-12-2019	☑	☐	☑	☑
928	Witteveen	1-1-1995	6-2-2000	☑	☐	☑	☑
929	Valthermond	8-2-2000	31-12-2019	☑	☐	☑	☑
934	Kollumerwaard	1-1-1995	31-12-2019	☑	☑	☑	☑
999	Niehove	24-9-1996	31-12-1999	☐	☐	☑	☐
NL49556	De Rijp-Oostdijkje	1-1-2012	31-12-2019	☑	☐	☐	☐
NL49565	Oude Meer-Aalsmeerderdijk	14-9-2010	31-12-2019	☑	☐	☑	☐
NL49703	Amsterdam – Spaarnwoude	1-1-2009	31-12-2019	☑	☑	☑	☐
Urban background							
137	Heerlen - Jamboreepad	28-8-2004	28-1-2014	☑	☑	☑	☑
138	Heerlen - Deken Nicolayestraat	26-11-2013	31-12-2019	☑	☑	☑	☑
241	Breda	23-2-2005	31-12-2019	☑	☑	☑	☑
242	Veldhoven-Rapportstraat	2009-01-01	2009-06-30	☐	☑	☐	☐
247	Veldhoven-Europalaan	2009-04-01	31-12-2019	☑	☑	☑	☑
404	Den Haag - Rebecquestraat	1-1-1995	31-12-2019	☑	☑	☑	☑
418	Rotterdam	1-1-1995	31-12-2019	☑	☑	☑	☑
442	Dordrecht	17-11-2010	31-12-2019	☑	☐	☑	☑
446	Den Haag-Bleriotlaan	14-12-2012	31-12-2019	☑	☐	☑	☑
518	Amsterdam-Cabeliaustraat	1-1-1995	23-5-2004	☑	☐	☑	☐
520	Amsterdam - Florapark	1-1-1995	1-1-2013	☑	☐	☑	☑
549	Laren	21-2-2008	22-1-2018	☑	☐	☑	☐
640	Utrecht - Universiteitsbibliotheek	1-1-1995	30-9-2004	☐	☐	☑	☑
643	Utrecht-Griftpark	5-1-2013	31-12-2019	☐	☑	☑	☑
742	Amsterdam-Overtoom	1-10-2008	31-12-2019	☐	☑	☐	☐
820	Enschede-Espoortstraat	1-1-2009	16-8-2010	☐	☑	☐	☐
821	Enschede-Winkelhorst	23-6-2010	31-12-2019	☐	☑	☐	☐
938	Groningen	30-6-2005	31-12-2019	☐	☑	☐	☑
NL49003	Amsterdam-Nieuwendammerdijk	1-1-2003	31-12-2019	☐	☐	☑	☑
NL49014	Amsterdam-Vondelpark	1-1-2003	31-12-2019	☑	☑	☑	☑
NL49016	Amsterdam-Westerpark	1-1-2010	31-12-2019	☑	☑	☐	☐
NL49561	Badhoevedorp-Sloterweg	1-1-2003	31-12-2019	☑	☑	☑	☐

Site ID	Site name	Start date*	End date*	PM10	PM2.5	NO_2	O_3
NL49564	Hoofddorp-Hoofdweg	1-1-2003	31-12-2019	☑	☐	☑	☑
NL49701	Zaandam-Wagenschotpad	5-5-2006	31-12-2019	☑	☑	☑	☐
NL49019	Amsterdam-Oude Schans	5-1-2007	26-12-2019	☐	☐	☑	☐
NL49021	Amsterdam-Kantershof	15-1-2007	31-12-2019	☐	☐	☑	☑
NL49022	Amsterdam-Sportpark Ookmeer	26-1-2007	31-12-2019	☐	☐	☑	☑
NL49570	Beverwijk West-Creutzberglaan	1-1-2011	31-12-2019	☑	☑	☐	☐
NL01485	Hoogvliet	1-1-2003	31-12-2019	☑	☑	☑	☑
NL01494	Schiedam	1-1-2003	31-12-2019	☑	☑	☑	☑
NL01486	Pernis	1-1-2008	29-2-2016	☑	☐	☑	☐
NL01488	Rotterdam Zuid	1-1-2010	31-12-2019	☑	☑	☑	☐

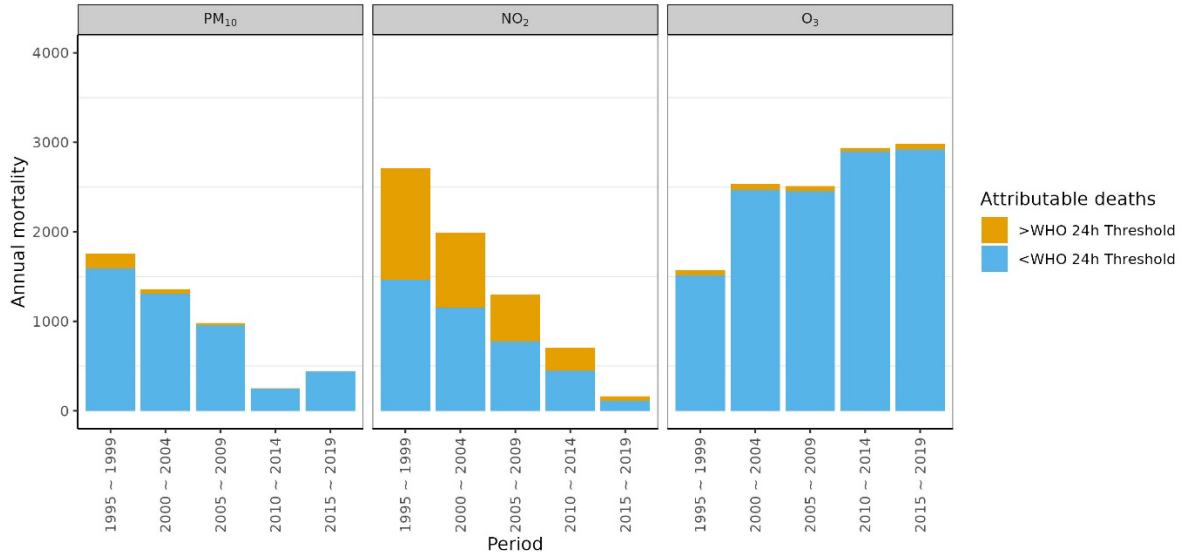
* The start- and end date of the monitoring location can vary between pollutants. Details per pollutant can be obtained from: https://data.rivm.nl/data/luchtmeetnet/metadata/

Table A2 Frequency of low, moderate and high birch, grass and weed pollen concentrations in the Netherlands between 1995 and 2019.

	Low[a] N (%)	Medium[b] N (%)	High[c] N (%)
Birch	8230 (91%)	521 (6%)	336 (4%)
Grasses	7233 (79%)	910 (10%)	958 (11%)
Weeds	8456 (93%)	576 (6%)	89 (1%)

a: Low = Less than 10 grains/m^3
b: Moderate = 10-100 grains for birch and 10-30 grains/m^3 for grasses and weeds
c: High = More than 100 grains for birch and more than 30 grains/m^3 for grasses and weeds

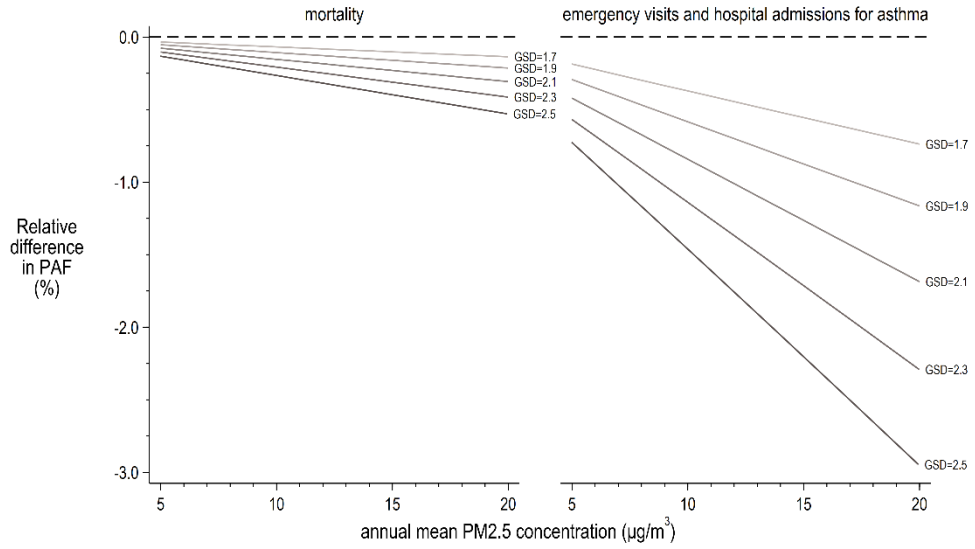
Figure A1 Excess mortality per year associated with air pollution below and above the recommended short-term Air Quality Guideline (AQG) levels (WHO, 2021) per component (PM10, NO2 and O3) and 5yr-time interval (1995-1999, 2000-2004, 2005-2009, 2010-2014, 2015-2019). The short-term AQG levels were: PM10 - 45 µg/m³ (24-hour average), NO_2 - 25 µg/m³ (24-hour average) and O_3 - 100 µg/m³ (8-hour max).



Appendix 2

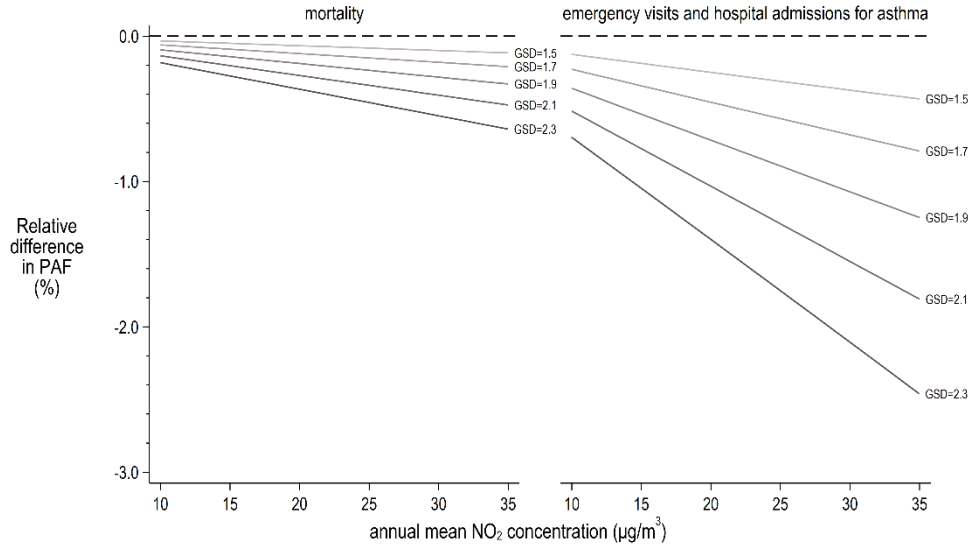
The annual GSD for PM2.5 varied concentration in 2008-2019 between 1.76 and 2.54 with an average around 2.0. The annual average of the 24-hour mean was between 12 and 14 µg/m^3, with a maximum of 18 µg/m^3. We simulated the daily exposure with a GSD varying between 1.47 and 2.5 and with an annual mean concentration between 5 and 20 µg/m^3.

Figure A2 Relative underestimation of PAF (%) for mortality and emergency visits and hospital admissions attributed to PM2.5 exposure due to the average risk approach at different simulated concentrations and geometric standard deviations (GSDs).



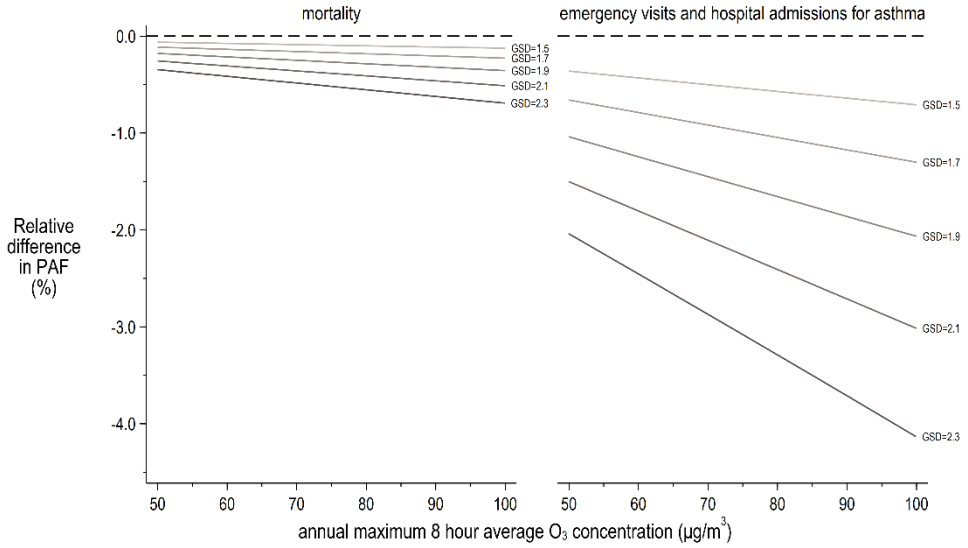
The annual GSD varied for NO_2 in 1995-2019 between 1.48 and 2.27, with an average of about 1.70. The annual average was between 15 and 27 µg/m^3 and could increase to 34 µg/m^3. We simulated exposure distribution with a GSD varying between 1.5 and 2.3 and with an annual mean concentration between 10 and 35 µg/m^3.

Figure A3 Relative underestimation of PAF (%) for mortality and emergency visits and hospital admissions attributed to NO_2 exposure due to the average risk approach at different simulated concentrations and geometric standard deviations (GSDs).



The average annual GSD for O_3 for the four regions of the Netherlands was in the period 1995-2019 between 1.7 and 1.95; the annual values varied between 1.45 and 2.35. The annual average of the maximum 8-hour mean concentration was between 61 and 66 µg/m^3 and could increase to 71 µg/m^3.
As input for the simulation of O_3 distributions, we varied the GSD between 1.5 and 2.3 and the annual concentration between 50 and 100 µg/m^3, as O_3 concentrations are expected to increase in the coming decades due to climate change.

Figure A4 Relative underestimation of PAF (%) for mortality and emergency visits and hospital admissions attributed to O_3 exposure due to the average risk approach at different simulated concentrations and geometric standard deviations (GSDs).



Published by

National Institute for Public Health and the Environment, RIVM
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

November 2025

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