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Long term exposure to road traffic noise and air pollution and risk of infertility in men and women: nationwide Danish cohort study

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ABSTRACT

OBJECTIVES

To investigate associations between long term residential exposure to road traffic noise and particulate matter with a diameter <2.5 µm ($PM_{2.5}$) and infertility in men and women.

DESIGN

Nationwide prospective cohort study.

SETTING

Denmark.

PARTICIPANTS

526 056 men and 377 850 women aged 30-45 years, with fewer than two children, cohabiting or married, and residing in Denmark between 2000 and 2017.

MAIN OUTCOME MEASURE

Incident infertility in men and women during follow-up in the Danish National Patient Register.

RESULTS

Infertility was diagnosed in 16 172 men and 22 672 women during a mean follow-up of 4.3 years and 4.2 years, respectively. Mean exposure to $PM_{2.5}$ over five years was strongly associated with risk of infertility in men, with hazard ratios of 1.24 (95% confidence interval 1.18 to 1.30) among men aged 30-36.9 years and 1.24 (1.15 to 1.33) among men aged 37-45 years for each interquartile (2.9 µg/m^3) higher $PM_{2.5}$ after adjustment for sociodemographic variables and road traffic noise. $PM_{2.5}$ was not associated with infertility in women. Road traffic noise (Lden, most exposed facade of residence) was associated with a higher risk of infertility among women aged 35-45 years, with a hazard ratio of 1.14 (1.10 to 1.18) for each interquartile (10.2 dB) higher five year mean exposure. Noise was not associated with infertility among younger women (30-34.9 years). In men, road traffic noise was associated with higher risk of infertility in the 37-45 age group (1.06, 1.02 to 1.11), but not among those aged 30-36.9 years (0.93, 0.91 to 0.96).

CONCLUSIONS

$PM_{2.5}$ was associated with a higher risk of an infertility diagnosis in men, whereas road traffic noise was associated with a higher risk of an infertility diagnosis in women older than 35 years, and potentially in men older than 37 years. If these results are confirmed in future studies, higher fertility could be added to the list of health benefits from regulating noise and air pollution.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Particulate air pollution and transportation noise are the two largest environmental causes of disease and death

Particulate air pollution has been associated with reduced sperm quality and reduced success of fertility treatment, whereas results on fecundability are inconsistent

Although one study found road traffic noise to increase time to pregnancy, no studies have investigated the effects of transportation noise on incident infertility in men and women

WHAT THIS STUDY ADDS

Exposure to particulate air pollution was associated with an increased risk of an infertility diagnosis in men

Road traffic noise was associated with a higher risk of an infertility diagnosis among women older than 35 years, and potentially among men older than 37 years

If these findings are confirmed in future studies, they may prove important in guiding decision makers responsible for setting priorities and implementing mitigations strategies to protect the general population from these exposures

Introduction

Infertility is a major global health problem affecting one in seven couples trying to conceive.[1] Infertility affects all geographical areas of the world, with some of the highest rates observed in south and central Asia, sub-Saharan Africa, the Middle East, north Africa, and central and eastern Europe.[2] Infertility is defined as lack of conception after one year of regular, unprotected sexual intercourse.[3] The use of various assisted reproductive technologies has increased noticeably since the 1980s, and more than 10 million children have been conceived using such technologies worldwide.[4] Infertility in both men and women is associated with various long term adverse health effects, including shorter life expectancy and increased risk of various psychiatric disorders and somatic diseases.[5 6] Furthermore, infertility is often a harsh experience, with a high level of physical and psychological strain, including high stress levels, anxiety, and symptoms of depression.[7 8]

Many of the established risk factors for infertility are similar for men and women and include advanced age (especially for women, where fertility drops rapidly after the late 30s), tobacco and alcohol use, sexually transmitted infections, various chronic conditions and diseases, obesity, and severe underweight.[9] In addition, exposure to environmental factors, such as air pollution, pesticides, and ionising radiation, are suspected risk factors for infertility.[10] Ambient air pollution is a major environmental pollutant causing cardiometabolic and respiratory morbidity and mortality.[11 12] Furthermore, during the past decade, epidemiological studies have found particulate air

pollution to be negatively associated with sperm quality, specifically lower sperm motility and count and changes in sperm morphology.[13-15] A growing number of studies have indicated that air pollution is also associated with a reduced success rate after fertility treatment in women,[16-20] although results are inconsistent.[21-23] In contrast, only a few studies have studied the effects of air pollution on infertility in women, with inconsistent results.[24-27] Also, these studies mainly investigated effects on fecundability, thus not capturing infertility in women directly, as fecundability can be influenced by infertility in both men and women.

Road traffic noise is another prevalent environmental pollutant that has been linked with various chronic diseases.[28-30] Health effects of noise are suggested to be mediated through the triggering of a stress response, with activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis,[31] as well as through sleep disturbance.[32] Both stress and sleep disturbance have been suggested to be associated with impaired reproductive function, including reduced sperm count and quality, menstrual irregularity, and impaired oocyte competence.[33-35] A main suggested biological pathway is activation of the hypothalamic-pituitary-adrenal axis, with release of stress hormones and inhibition of the hypothalamic-pituitary-gonadal axis, resulting in decreased levels of male and female sex hormones.[33-35] Only one study has investigated the effects of noise on fertility, specifically self-reported time to pregnancy in a cohort of ≈65 000 pregnant women, and the results indicated that road traffic noise was associated with an increased time to pregnancy.[36]

We investigated if long term exposure to road traffic noise and pollution from particulate matter air with a diameter <2.5 µm ($PM_{2.5}$) in the Danish population was associated with a higher risk of infertility in men and women, using individual level, time varying information on noise, air pollution, and socioeconomic variables and follow-up for infertility in the Danish National Patient Register.

Methods

Study population

Our study was based on all people residing in Denmark. Since 1968, all Danish inhabitants have been assigned a unique identification number, enabling linkage between administrative and health registers.[37] We used the Civil Registration System with exact address data for people in Denmark, including moving and migration dates, to find the address history from 1995 onwards.[37] We generated a study population for women and a study population for men and both study populations included people aged 30-45 years who were cohabiting or married, had fewer than two children, and lived in Denmark between 1 January 2000 and 31 December 2017 (n=377 850 women; 526 056 men). These inclusion criteria were implemented to obtain study populations with a high proportion of individuals who were actively trying to become pregnant, and thus under risk of receiving an infertility diagnosis.

Estimation of road traffic noise

We used the Building and Housing Register to obtain geocode and floor (for multistorey buildings) for all addresses in Denmark, and estimated road traffic noise at these addresses for 1995, 2000, 2005, 2010, and 2015 based on the validated Nordic prediction method.[38 39] Main traffic variables for the model were road type (motorway, express road, road wider than 6 m, road 3-6 m wide, and other road) and data on distributions of light and heavy vehicles, travel speed, and annual average daily traffic for all Danish roads.[40] We accounted for screening effects from all Danish buildings, noise barriers and terrain, reflections, and ground absorption. Noise was calculated as the equivalent A weighted sound pressure level for the day, evening, and night, and expressed as Lden. We estimated noise at the most and the least exposed facades of the residence at each address. Values <35 dB were set to 35 dB because noise below this level is unlikely to be discernible from background noise. We estimated yearly means for all addresses at all years between 1995 and 2017 using linear interpolation.

Estimation of air pollution

We assessed $PM_{2.5}$ at all addresses (ground level) using a validated modelling system comprising the Danish eulerian hemispheric model, the urban background model, and the operational street pollution model.[41-43] This system calculated $PM_{2.5}$ at all Danish addresses as the sum of air pollution at three different spatial scales: the regional background, estimated by a long range chemistry-transport model at 5.6-150 km^2 resolution (the Danish eulerian hemispheric model)[41]; local background, estimated in the urban background model covering Denmark in 1 km^2 resolutions[42]; and local street, calculated in the operational street pollution model, which takes into account traffic, street configurations, and emission factors.[43] All models include weather conditions calculated using the weather research and forecasting model.[44] The model system estimated hourly address specific concentrations of $PM_{2.5}$ during 2000, 2010, and 2015, which were summarised to yearly means for each of the three years. We subsequently calculated yearly means for each address for the period 1995-2017, based on yearly changes in urban background $PM_{2.5}$ estimated using the Danish eulerian hemispheric model and the urban background model.

Covariates

Covariates were selected based on availability in the Danish registers and plausibility to act as potential confounders (see supplementary figure S1). We collected yearly individual level information from 2000 to 2017 using national registers on individual income (sex and year standardised fifths), highest attained education (mandatory, secondary or vocational, or medium or long), occupational status (manual

worker, professional, or unemployed or retired), number of children (0 or 1), and country of birth (Denmark or other). We obtained yearly information on five neighbourhood level variables: Proportion of inhabitants in each parish (on average 16.2 km^2 and 1032 residents) with only mandatory education, low income, manual labour, and a criminal record, and as sole providers. We estimated population density in each parish (0-100, 100-5000, and >5000 individuals/km^3) and received information on house type for all addresses (single family house, semidetached house, apartment, or other).

Ascertainment of infertility

To assess infertility, we used personal identification numbers to link the two study populations of men and women with the Danish National Patient Register (valid since 1977), using ICD-8 and ICD-10 (international classification of diseases, eighth and 10th revisions, respectively) codes.[45] Infertility in women was registered as ICD-8 code 628 and ICD-10 code N97 (excluding N974: infertility in women due to male factors), and infertility in men was registered as ICD-8 code 606 (excluding 606.59, 606.80-89) and ICD-10 code N46 (excluding N469E: infertility in men after sterilisation). We only included the first registered infertility diagnosis. All individuals with a diagnosis of infertility before baseline were excluded. We also excluded women with tubal ligation, bilateral oophorectomy, or hysterectomy before baseline and men who were sterilised before baseline (see supplementary table S1 for operation codes). Furthermore, people undergoing any of these procedures during follow-up were censored at the date of the operation.

For analyses of infertility subtypes, we investigated anovulation (N970), tubal factor (N971), unspecified (N979), and a joint group of other causes of infertility in women (N972, N973, and N978) as subtypes of infertility in women, whereas azoospermia (N469B), oligospermia (N469C), and unspecified (N469) were included as subtypes of infertility in men. Low numbers for other infertility subtypes in men and women precluded meaningful analyses.

Statistical analyses

We analysed data using Cox proportional hazards models, with age as the underlying timescale, to calculate hazard ratios and 95% confidence intervals (CIs) for infertility in men and women (overall and for subtypes of infertility) for each interquartile range as well as for each 10 dB and 5 $\mu g/m^3$ increase in road traffic noise and $PM_{2.5}$, respectively. Exposure to both pollutants was modelled as time weighted five year running means, taking exposure at all addresses in the period into account (including moving), and entered as time varying variables into the Cox model, thus for each individual with infertility comparing with the five year mean exposure for all people without infertility at the same age as the individual with infertility at the time of diagnosis. Start of follow-up was defined as 30 years of age, 1 January 2000, or date of marriage or cohabiting, whichever came last, and the study populations were followed until date of infertility diagnosis, death, emigration, unknown address, bilateral oophorectomy (women only), tubal ligation (women only), hysterectomy (women only), sterilisation (men only), 45 years of age, divorce or end of cohabitation, birth of second child, or 31 December 2017, whichever came first.

We analysed data using three adjusted models. Model 1 included adjustment for calendar year (two year categories). In model 2, we further adjusted for highest attained education, individual level income, country of origin, occupation, and area level proportion of inhabitants with low income, only mandatory education, manual labour, and a criminal record, and as sole provider. In model 3, we additionally applied mutual adjustment for $PM_{2.5}$ and noise. All individual and area level covariates except country of origin were entered into the Cox models as yearly time varying variables (area level variables also changed with change of address).

We evaluated the assumption of proportional hazards for the three exposures by a correlation test between the scaled Schoenfeld residuals and the rank order of event time. We observed a strong deviation from the assumption for noise (noise at both the most and the least exposed facade) in the men and women study populations. To investigate this further, we calculated associations between the two noise exposures and infertility in men and women in the following age groups: 30-30.9, 31-31.9, 32-32.9, 33-33.9, 34-34.9, 35-35.9, 36-36.9, 37-37.9, 38-38.9, 39-39.9, 40-41.9, and 42-45 years (see supplementary figure S2 and tables S2 and S3). We observed that the hazard ratios differed across age groups, indicating a shift in hazard ratio levels around age 35 years for women and 37 years for men. Subsequent analyses were therefore conducted in the following age groups: 30-34.9 and 35-45 years for women and 30-36.9 and 37-45 years for men.

To investigate the shape of the exposure-response associations, we used natural cubic splines with three degrees of freedom. We furthermore analysed associations (model 3) in categories of noise at the most exposed facade (≤50, 50.01-55, 55.01-60, 60.01-65, and >65 dB) and $PM_{2.5}$ (≤12, 12.01-14, 14.01-16, and >16 $\mu g/m^3$).

For men aged 37-45 years and women aged 35-45 years we analysed associations separately among people: living at low (<100 people/km^2), medium (101-5000 people/km^2), or high (≥5000 people/km^2) population density; with a low, medium, or high level of education; with a personal income in the first, second, third, and fourth income group; and with 0 or 1 child, by including an interaction term in the model. Also, in analyses of noise at the most exposed facade, we investigated associations among people who had access to a silent facade with substantially lower noise levels than at the most exposed facade compared with people without a more silent facade (defined as a

difference between noise at the most and least exposed facades above and below 10.8 dB, corresponding to the median). In sensitivity analyses, we further adjusted for population density and type of residence.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), except tests for proportional hazards and the splines, which were done in R version 4.3.2.

Patient and public involvement

No patients were directly involved in defining the research question, in the study design, or in the analyses and reporting. A main reason was that the present study was conducted without any external funding, thus with limited resources to engage in patient and public involvement. However, discussions with citizens concerned about the effects of the environmental pollutants studied and with patients experiencing infertility and worrying about the causes helped to motivate initiation of the study.

Table 1 | Baseline sociodemographic and exposure characteristics among men and women in the study population. Values are number (percentage) unless stated otherwise

Baseline characteristics	Men (n=526 056)	Women (n=377 850)
Individual level		
Mean (SD) age (years)	33.6 (4.5)	32.7 (4.0)
Income level (fifth):		
Low (1)	86 153 (16.4)	58 988 (15.6)
Medium (2-4)	372 750 (70.8)	262 955 (69.6)
High (5)	67 153 (12.8)	55 907 (14.8)
Highest attained education:		
Mandatory education	106 491 (20.2)	54 537 (14.4)
Secondary or vocational education	305 702 (58.1)	183 266 (48.5)
Medium or long education	113 863 (21.6)	140 047 (37.1)
Country of origin:		
Denmark	520 385 (98.9)	375 064 (99.3)
Other	5671 (1.1)	2786 (0.7)
Occupational status:		
Manual worker	290 411 (55.2)	164 656 (43.6)
Professional	194 934 (37.1)	167 360 (44.3)
Retired or unemployed	40 711 (7.7)	45 834 (12.1)
No of children:		
0	317 920 (60.4)	176 957 (46.8)
1	208 136 (39.6)	200 893 (53.2)
Area level		
Mean (SD) area level SES (%):		
Low income	5.2 (2.6)	5.2 (2.7)
Only mandatory education	10.5 (3.9)	10.0 (3.8)
Manual labour	12.9 (4.1)	12.6 (4.1)
Criminal record	0.56 (0.36)	0.55 (0.35)
Sole providers	5.4 (1.8)	5.5 (1.8)
Population density (people/km^3):		
<100	112 993 (21.5)	70 725 (18.7)
100-5000	318 378 (60.5)	231 207 (61.2)
≥5000	94 685 (18.0)	75 918 (20.1)
Address level		
House type:		
Single family	247 298 (47.0)	177 643 (47.0)
Semi-detached	55 377 (10.5)	42 461 (11.2)
Apartment	222 280 (42.3)	157 030 (41.6)
Other	1101 (0.2)	716 (0.2)
Mean (SD) exposures at 5 years:		
Noise, most exposed facade (dB)	58.6 (7.4)	58.9 (7.2)
Noise, least exposed facade (dB)	46.5 (6.1)	46.8 (5.9)
$PM_{2.5}$ (μg/m^3)	15.5 (2.2)	15.5 (2.3)

Results

Of 1 133 142 men and 1 090 344 women aged between 30 and 45 years (2000-17) identified, we excluded 12 654 men with an infertility diagnosis or sterilisation before baseline, and 85 700 women with an infertility diagnosis, bilateral oophorectomy, tubal ligation, or hysterectomy before baseline. We further excluded 310 940 men and 458 002 women who had two or more children (or with missing information) at time of enrolment, and 222 796 men and 123 188 women who did not live with a partner at any time during follow-up or were in a same sex registered partnership (or with missing information). We also excluded 30 395 men and 21 872 women with an incomplete address history five years before baseline, and 30 301 men and 23 732 women lacking information on any covariates. This resulted in study populations of 526 056 men and 377 850 women of whom 16 172 men and 22 671 women had an infertility diagnosis during a mean follow-up of 4.3 years and 4.2 years, respectively.

Table 1 shows the baseline sociodemographic and exposure characteristics of the two study populations. Distributions of exposure and median levels of noise and $PM_{2.5}$ as well as correlations between exposures were similar among men and women (table 1, also see supplementary figure S3). Noise at the most and least exposed facades were moderately correlated, with Spearman correlation coefficient (Rs) for women of 0.38, whereas correlations between noise and $PM_{2.5}$ were low, with Rs between 0.05 and 0.16 (see supplementary table S4). Median five year mean $PM_{2.5}$ levels decreased in the study population during the follow-up period, from 17.3 μg/m^3 in 2000 to 12.1 μg/m^3 in 2017, whereas five year mean noise levels increased slightly from 57.7 dB in 2000 to 59.1 dB in 2017 (see supplementary table S5). Owing to highly non-linear associations between noise at the least exposed facade and infertility in both men and women, we did not conduct further analyses with this noise measure as a continuous variable (see supplementary figure S4).

Among men, we observed that exposure to $PM_{2.5}$ was associated with a higher risk of infertility, with similar sized hazard ratios in the two investigated age groups (30-36.9 and 37-45 years) in the fully adjusted model 3 (table 2). The categorical analyses (table 3) and splines (fig 1) showed that the associations followed linear exposure-response associations throughout the exposure range. For noise, we observed no association with infertility in men in the youngest age group (30-36.9 years) before adjustment for $PM_{2.5}$ (model 2), whereas after adjustment, noise was associated with a hazard ratio of <1 (model 3, table 2). In the oldest age group (37-45 years), noise was associated with a slightly higher risk of infertility in men both before and after adjustment for $PM_{2.5}$. For both exposures, further adjustment for population density and type of residence resulted in only small changes in hazard ratios (see supplementary table S6). After further adjustment for children (0 or 1) the hazard ratio for noise was reduced in the 37-45 age group, from 1.06

Table 2 | Associations between an interquartile range higher five year mean road traffic noise at the most exposed facade and air pollution ($PM_{2.5}$) in relation to infertility in men and women in two age groups

Exposures	Age group (years)	No with infertility	Hazard ratio (95% CI)*		
			Model 1†	Model 2‡	Model 3§
Infertility in men					
Noise¶	30-36.9	11 542	0.98 (0.96 to 1.01)	0.98 (0.95 to 1.01)	0.93 (0.91 to 0.96)
Noise¶	37-45	4630	1.13 (1.09 to 1.18)	1.11 (1.06 to 1.15)	1.06 (1.02 to 1.11)
$PM_{2.5}$	30-36.9	11 542	1.20 (1.15 to 1.25)	1.18 (1.13 to 1.24)	1.24 (1.18 to 1.30)
$PM_{2.5}$	37-45	4630	1.37 (1.28 to 1.46)	1.28 (1.20 to 1.38)	1.24 (1.15 to 1.33)
Infertility in women					
Noise¶	30-34.9	14 752	0.91 (0.89 to 0.93)	0.97 (0.95 to 1.00)	0.98 (0.96 to 1.01)
Noise¶	35-45	7920	1.18 (1.15 to 1.22)	1.15 (1.11 to 1.18)	1.14 (1.10 to 1.18)
$PM_{2.5}$	30-34.9	14 752	0.84 (0.81 to 0.87)	0.94 (0.91 to 0.98)	0.95 (0.91 to 1.00)
$PM_{2.5}$	35-45	7920	1.20 (1.14 to 1.26)	1.13 (1.07 to 1.19)	1.04 (0.98 to 1.10)

CI=confidence interval; $PM_{2.5}$=fine particulate matter with a diameter <2.5 µm.
*Hazard ratios with 95% confidence intervals per interquartile range higher noise at the most exposed facade (10.2 dB), and $PM_{2.5}$ (2.9 µg/m^3).
†Adjusted for age (by design) and calendar year.
‡Model 1 plus adjustment for highest attained education, country of origin, occupation, personal income, and five area level socioeconomic variables: proportion of people with low income, only mandatory education, manual labour, criminal record, and as sole provider.
§Model 2 plus adjustment for mutual $PM_{2.5}$ and noise at the most exposed facade.
¶Road traffic noise (Lden) at the most exposed facade.

(95% CI 1.02 to 1.11) to 1.02 (0.98 to 1.07), whereas the association with $PM_{2.5}$ remained unchanged (see supplementary table S6).

Among women, noise was associated with a higher risk of infertility in the 35-45 age group, whereas no association was observed in the 30-34.9 age group (table 2). The association with noise in the oldest age group followed a close to linear exposure-response association, although at high exposures (>65 dB) the association levelled off (table 3, fig 1). Exposure to $PM_{2.5}$ was not associated with higher risk of infertility in women in any of the investigated age groups. For both exposures, further adjustment for population density, type of residence, and number of children resulted in only slight changes in hazard ratios (see supplementary table S6).

When investigating the effects of the two exposures on infertility subtypes in women, we found that noise was associated with a higher risk of all three subtypes investigated (anovulation, tubal factor, and unknown cause) in the 35-45 age group but not in the 30-34.9 age group, whereas $PM_{2.5}$ was associated with higher

Table 3 | Association between five year exposure to road traffic noise and $PM_{2.5}$ and risk of infertility in men and women in categories of exposure and per 10 dB and 5 µg/m^3 higher noise and $PM_{2.5}$, respectively

Exposures	Infertility in men			Infertility in women		
	Age group	No with infertility	Model 3*: hazard ratio (95% CI)	Age group	No with infertility	Model 3*: hazard ratio (95% CI)
Noise, most exposed facade (Lden)						
≤50 dB	30-36.9	1532	1.00 (ref)	30-34.9	1944	1.00 (ref)
50.01-55 dB	30-36.9	1794	0.96 (0.89 to 1.02)	30-34.9	2276	0.96 (0.91 to 1.02)
55.01-60 dB	30-36.9	2889	0.90 (0.85 to 0.96)	30-34.9	3821	0.96 (0.90 to 1.01)
60.01-65 dB	30-36.9	3033	0.88 (0.83 to 0.94)	30-34.9	4041	0.97 (0.90 to 1.02)
>65 dB	30-36.9	2294	0.90 (0.84 to 0.97)	30-34.9	2670	0.96 (0.90 to 1.02)
Linear, per 10 dB	30-36.9	11 542	0.94 (0.91 to 0.96)	30-34.9	14 752	0.98 (0.96 to 1.01)
≤50 dB	37-45	711	1.00 (ref)	35-45	1088	1.00 (ref)
50.01-55 dB	37-45	819	1.20 (1.08 to 1.33)	35-45	1317	1.20 (1.11 to 1.31)
55.01-60 dB	37-45	1188	1.21 (1.10 to 1.32)	35-45	2099	1.32 (1.23 to 1.42)
60.01-65 dB	37-45	819	1.24 (1.13 to 1.37)	35-45	2051	1.35 (1.25 to 1.46)
>65 dB	37-45	711	1.16 (1.04 to 1.29)	35-45	1365	1.36 (1.25 to 1.49)
Linear, per 10 dB	37-45	4630	1.06 (1.02 to 1.10)	35-45	7920	1.13 (1.10 to 1.17)
Particulate air pollution, $PM_{2.5}$						
≤12 µg/m^3	30-36.9	1644	1.00 (ref)	30-34.9	1746	1.00 (ref)
12.01-14 µg/m^3	30-36.9	3622	1.28 (1.20 to 1.37)	30-34.9	3688	1.10 (1.03 to 1.18)
14.01-16 µg/m^3	30-36.9	3982	1.31 (1.20 to 1.43)	30-34.9	5683	1.01 (0.93 to 1.10)
>16 µg/m^3	30-36.9	2294	1.46 (1.32 to 1.62)	30-34.9	3635	0.97 (0.88 to 1.06)
Linear, per 5 µg/m^3	30-36.9	11 542	1.44 (1.33 to 1.57)	30-34.9	14 752	0.92 (0.86 to 0.99)
≤12 µg/m^3	37-45	771	1.00 (ref)	35-45	1068	1.00 (ref)
12.01-14 µg/m^3	37-45	1431	1.24 (1.12 to 1.38)	35-45	1897	0.99 (0.91 to 1.08)
14.01-16 µg/m^3	37-45	1578	1.37 (1.20 to 1.57)	35-45	3116	1.12 (1.00 to 1.25)
>16 µg/m^3	37-45	850	1.57 (1.34 to 1.84)	35-45	1839	1.12 (0.98 to 1.27)
Linear, per 5 µg/m^3	37-45	4630	1.44 (1.27 to 1.64)	35-45	7920	1.07 (0.97 to 1.18)

CI=confidence interval; $PM_{2.5}$=fine particulate matter with a diameter <2.5 µm.
*Adjusted for age (by design), calendar year, highest attained education, country of origin, occupation, personal income, and five area level socioeconomic variables: proportion of people with low income, only mandatory education, manual labour, criminal record, and as sole provider, and mutual $PM_{2.5}$ and noise at the most exposed facade adjustment.

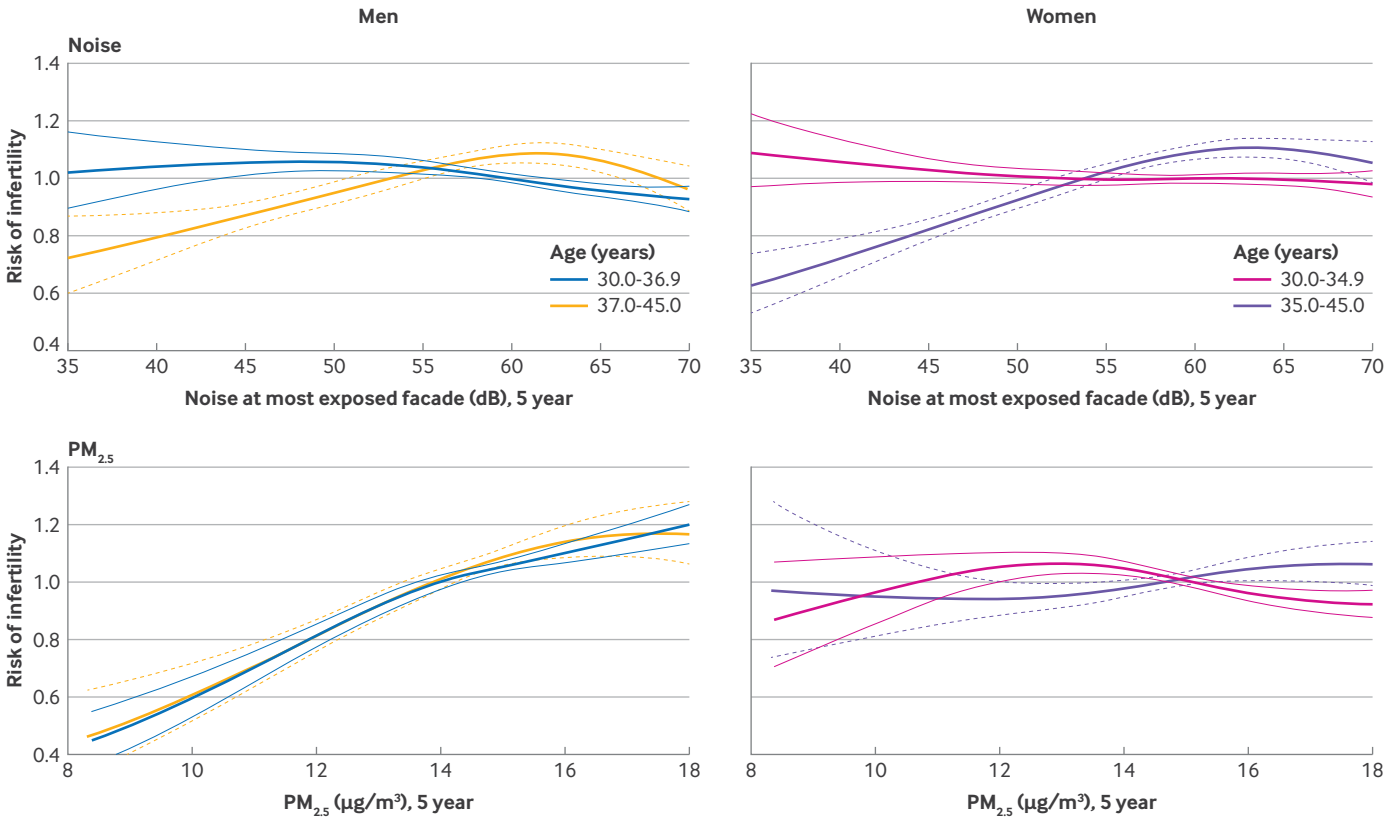

Fig 1 | Splines showing association between five year mean residential exposure to road traffic noise at the most exposed façade at home and $PM_{2.5}$ and risk of infertility in men and women in groups according to age in the fully adjusted model 3. dB=decibel; $PM_{2.5}$=fine particulate matter with a diameter <2.5 µm

risk of unknown infertility in both age groups (table 4). For subtypes of infertility in men, we observed positive associations between $PM_{2.5}$ and the three subtypes investigated (oligospermia, azoospermia, and unknown infertility) in both age groups. Noise seemed to be associated with a reduced risk of azoospermia (although based on only 273 people) and unknown infertility in men in the 30-36.9 age group and a higher risk of unknown infertility in men in the 37-45 age group.

We found similar hazard ratios between the two exposures and infertility in women and between $PM_{2.5}$ and infertility in men across areas of low, median, and high population density; low, median, and high individual level education; and fourths of personal income, whereas for noise and infertility in men, associations were only observed among men living in low and median population densities, with low or medium educational level, or with income above the lowest fourth, or a combination of these (fig 2, see supplementary table S7). When comparing hazard ratios across people with no children or one child, we observed similar hazard ratios for both exposures in relation to infertility in men, whereas for infertility in women, noise was only associated with higher risk for primary infertility (for secondary infertility we observed a hazard ratio <1) and $PM_{2.5}$ was only associated with a higher risk of secondary infertility (fig 2, see supplementary table S7).

When investigating the association between noise at the most exposed facade and infertility among people with a large versus a small difference between noise level at the most and least exposed facades, we observed stronger associations only when a small difference in noise existed between the two facades, corresponding to having "no silent facade" (fig 2, see supplementary table S7).

Discussion

Based on a large nationwide, prospective cohort, designed to include a high proportion of people actively trying to achieve pregnancy, we found that mean five year exposure to noise was associated with a higher risk of infertility among women aged between 35 and 45 years, whereas no associations were observed between $PM_{2.5}$ and infertility in women. The association between noise and infertility in women seemed confined to those without children (primary infertility). For men, we observed that five year exposure to $PM_{2.5}$ was associated with a higher risk of infertility across the investigated age range (30-45 years), and noise seemed weakly associated with infertility among men aged 37-45 years. The higher risk of noise related infertility in women and $PM_{2.5}$ related infertility in men was consistent across people living in rural, suburban, and urban areas as well as across people with low, medium, and high socioeconomic status. For noise, we

Table 4 | Associations between an interquartile range higher five year mean road traffic noise at the most exposed facade and $PM_{2.5}$ in relation to subtypes of infertility in men and women

Infertility subtypes by age group (years)	No with infertility	Hazard ratio (95% CI)*†	
		Noise, most exposed facade	$PM_{2.5}$
Women			
Anovulation:			
30-34.9	852	1.03 (0.92 to 1.14)	0.72 (0.59 to 0.87)
35-45	272	1.21 (1.01 to 1.44)	0.91 (0.66 to 1.26)
Tubal factor:			
30-34.9	748	1.09 (0.97 to 1.23)	0.96 (0.80 to 1.17)
35-45	493	1.31 (1.14 to 1.52)	0.98 (0.79 to 1.22)
Unspecified:			
30-34.9	9042	0.95 (0.92 to 0.99)	1.08 (1.03 to 1.15)
35-45	4881	1.11 (1.07 to 1.16)	1.13 (1.05 to 1.22)
Others:			
30-34.9	4147	1.04 (0.99 to 1.09)	0.75 (0.69 to 0.82)
35-45	2323	1.15 (1.08 to 1.23)	0.88 (0.79 to 0.98)
Men			
Oligospermia:			
30-36.9	1196	0.93 (0.85 to 1.01)	1.31 (1.12 to 1.55)
37-45	521	1.01 (0.90 to 1.14)	1.36 (1.07 to 1.72)
Azoospermia:			
30-36.9	273	0.82 (0.68 to 0.98)	1.45 (1.06 to 1.99)
37-45	145	0.87 (0.70 to 1.10)	1.08 (0.70 to 1.68)
Unspecified:			
30-36.9	9723	0.95 (0.92 to 0.99)	1.18 (1.12 to 1.25)
37-45	4364	1.10 (1.05 to 1.14)	1.19 (1.10 to 1.28)

CI=confidence interval; $PM_{2.5}$=fine particulate matter with a diameter <2.5 µm.
*Adjusted for age, calendar year, highest attained education, country of origin, occupation, personal income, cohabiting status, five area level socioeconomic variables (proportion of people with low income, only mandatory education, manual labour, criminal record, and as sole provider), and mutual $PM_{2.5}$ and noise at the most exposed facade adjustment.
†Hazard ratios with 95% confidence intervals per interquartile range higher noise at the most exposed facade (10.2 dB) and $PM_{2.5}$ (2.9 µg/m^3).

observed stronger associations with infertility among people without a silent facade at home.

Strengths and limitations of this study

Strengths of this study include the nationwide design, with low risk of selection bias, together with a high number of people with incident infertility identified from high quality registers during a follow-up period of 18 years. To optimise the likelihood of obtaining valid and unbiased results, we restricted the study population to include a high proportion of people who were at risk of an infertility diagnosis—that is, those who were actively trying to become pregnant. Accordingly, our study population included men and women aged 30-45 years who were married or cohabiting. Furthermore, all study participants were censored at the time they had their second child. This censoring criterion was applied because Danish women on average gave birth to 1.8 children during the study period and therefore it is likely that after the birth of a second child, many couples no longer try for pregnancy. Although applying these restriction criteria increased the probability that a large proportion of our study population were trying to become pregnant, it was inevitable that our cohort also included couples who were not—for example, couples prioritising their career before children. This is a limitation of the study design.

People with infertility were identified using the high quality Danish National Patient Register, which has high validity and completeness of diagnoses in Denmark.[46] Thus, only infertile couples actively seeking infertility counselling were identified as infertile participants in the study. In Denmark, however, all inhabitants can seek infertility counselling and fertility treatment free of charge, and the procedures are standardised across Denmark, starting with a visit to the general practitioner who, if infertility is suspected, refers individuals to a fertility clinic. As Denmark is a small country, the distance between home and a fertility clinic is not expected to be an obstacle to seeking fertility treatment, and we did not expect major differences in the likelihood of obtaining an infertility diagnosis according to geographical location alone.

Another important strength was that we had access to an exact history of residential address for all participants from five years before baseline until end of follow-up, linked with exposure to both road traffic noise and $PM_{2.5}$ estimated used validated exposure models and high quality input data.[43 47] As these two exposures are correlated and found to be associated with many of the same diseases, mutual adjustment was crucial.

As the present study was based entirely on register data, we did not have information on lifestyle factors, such as alcohol use, smoking, and body mass index, which is a limitation. We did, however, have access to detailed time varying register based information on individual and neighbourhood level sociodemographic variables, enabling us to adjust for key socioeconomic covariates, thereby indirectly adjusting for lifestyle. That our adjustment strategy may sufficiently capture lifestyle confounding is supported by results from our previous studies on noise and air pollution and risk of cardiovascular disease, diabetes, and mortality, which were based on large Danish questionnaire based cohorts with detailed information on lifestyle.[48-50] These studies showed that after adjusting for the socioeconomic variables included in the present study, further adjustment for lifestyle had only a minimal effect on the risk estimates. Another limitation is lack of information on exposure to noise and $PM_{2.5}$ at work and at leisure time activities away from home. This may affect the size and statistical precision of risk estimates owing to a mixture of classic and Berkson error.

Comparison with other studies

In support of our results on $PM_{2.5}$ and infertility in men, particulate air pollution ($PM_{2.5}$ and PM_{10}) has in recent studies been found to be negatively associated with factors defining sperm quality, including sperm motility and count as well as changes in sperm morphology.[13-15] Our study therefore adds to these findings, showing that the effects of air pollution on sperm quality will potentially result in a higher risk of requiring assistance from a fertility clinic to achieve pregnancy. Interestingly, we found that the association between air pollution and infertility in men followed a linear exposure-response association, starting from around ≥8.5 µg/m^3 in both investigated age groups, indicating that even at the relatively low levels of $PM_{2.5}$

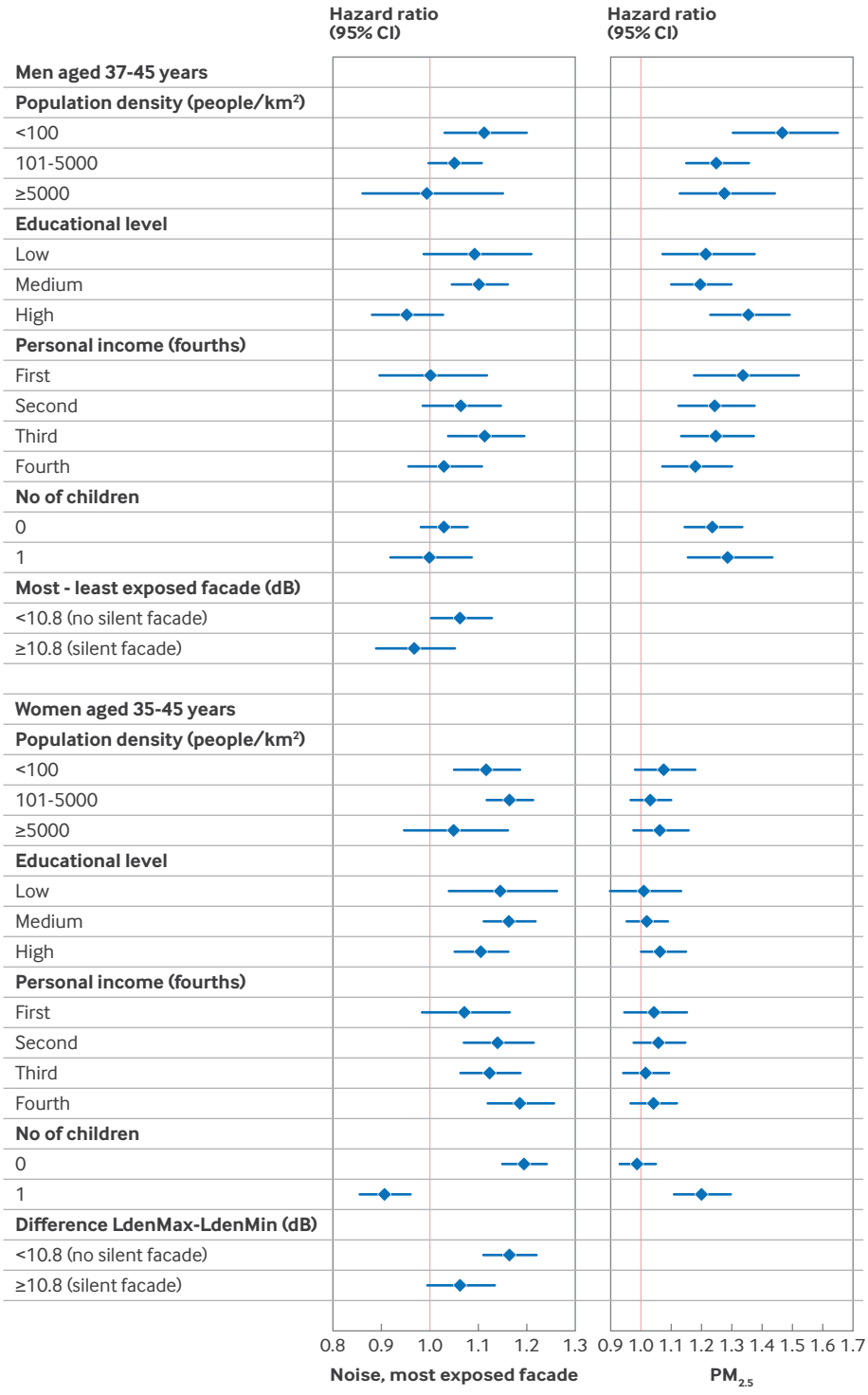

Fig 2 | Associations between an interquartile range higher five year mean road traffic noise and $PM_{2.5}$ and risk of infertility among men aged 37-45 years and women aged 35-45 years, according to population density, education, personal income, number of children, and access to a silent façade at home. CI=confidence interval; dB=decibel; $PM_{2.5}$=fine particulate matter with a diameter <2.5 µm

found in Denmark, particulate air pollution can reduce fertility in men.

For women, most previous studies have focused on investigating effects of air pollution on success of fertility treatment among couples referred to fertility clinics.[16-23] Although most studies found particulate matter air pollution to be associated with, for example, a reduced likelihood of clinical pregnancy, live birth after fertility treatment, and odds of receiving fertility treatment,[16-20] others found no association.[21-23] Also, the few studies investigating the effects of short term or long term, or both, exposure to air pollution

on fecundability (assessed as time to pregnancy) have provided inconsistent results.[25-27] However, fecundability can be influenced by infertility in both men and women, and therefore results are difficult to interpret in the context of infertility in women, as a positive association can potentially be driven by effects of air pollution on semen quality. The results from these previous studies can therefore not be directly compared with the present study, where we have direct and differentiated measures of infertility in men and women. However, in a study based on 36 000 women from the Nurses' Health Study II with self-reported follow-up for infertility (defined as attempting conception for ≥12 months), the authors were able to distinguish between infertility in men and women in 27% of women with fertility problems.[24] In both main analyses (couple based infertility) and analyses restricted to infertility in women, the authors reported that long term exposure to $PM_{2.5}$ (four year mean) was not associated with higher risk of infertility, which agrees with the results of the present study.

A potential explanation as to why we found $PM_{2.5}$ exposure associated with infertility in men and not women is that while female follicle development begins in utero, new sperm cells are produced continuously in the testis (after puberty), with an overall lifespan of three months. Therefore, particulate air pollution may act directly on the sperm cells during the vulnerable spermatogenesis phase—for example, through direct toxic effects of particles translocated from the lungs into the blood, oxidative stress, inflammatory processes, and genotoxicity.[51 52] In contrast, the potential biological mechanisms underlying an association between air pollution and infertility in women are less established but have been hypothesised to involve some of the same pathogenetic mechanisms as described for infertility in men as well as endocrine disrupting properties caused by air pollutants mimicking the effect of androgens and oestrogens.[53]

The only previous study on traffic noise and a fertility related outcome indicated that among 65 000 pregnant women, road traffic noise was associated with a higher risk of trying for six months or more to achieve pregnancy (self-reported) compared with getting pregnant within six months.[36] This indicates that noise may impact fecundity, which supports the findings of the present study—although the two studies are not directly comparable, as the previous study focused on self-reported time to pregnancy among pregnant women, whereas the present study investigated risk of receiving a diagnosis of infertility. A potential explanation as to why we only observed an association with noise among women older than 35 years is that many who are trying to become pregnant in this age group are likely to be in a more stressful state than women in a younger age group if pregnancy is not achieved immediately, as it is well known that fertility drops steeply in women in their late 30s.[54] Therefore, women in this age group may be more susceptible to noise induced stress and sleep disturbance,[31 32] as they are potentially already in a state of distress. In support, we only observed a positive association with noise among women with primary infertility, who are expected to be in a more stressful state than women who already have one child (secondary infertility). It is established that infertility is associated with psychological symptoms, such as depression and distress, especially among women.[33 55] It is still, however, unclear whether stress is a risk factor for infertility.[33] Our finding of an association between noise and infertility only among women older than 35 years may also be partly explained by different underlying causes of infertility across age groups. For example, somatic disorders known to be important causes of infertility in women, such as endometriosis and polycystic ovary syndrome, are often diagnosed at a relatively early age and people with these disorders are thus more likely to contact fertility clinics for counselling at an earlier age. As we hypothesised that noise would have only a minor or no impact on the risk of infertility among individuals with a definite somatic cause of infertility, this may at least partly explain why we observed no association between noise and infertility in women in the 30-35 age group.

Among men, we observed that noise was associated with a lower risk of infertility in the 30-36.9 age group and a higher risk in the 37-45 age group. The biologically implausible lowering of risk in the youngest age group was, however, driven by adjustment for $PM_{2.5}$, suggesting that this was an artefact. In the 37-45 age group, the association was robust to adjustment for $PM_{2.5}$ as well as to adjustment for population density, suggesting that noise may be a risk factor for infertility in men. After adjustment for number of children, however, the association was no longer present. More studies are needed to establish whether noise is a risk factor for infertility in men—for example, studies on noise and semen quality.

To investigate the robustness of our results, we examined whether our main findings were consistent across urban, suburban, and rural areas. In Denmark, couples who are considering starting a family are likely to move from apartments in larger cities to single family houses in suburban or rural areas, which in most instances will result in reduction of exposure to air pollution and noise. Although we had detailed information on changes of address (and exposure) for all participants, this could have potentially biased our results. However, the observed associations between $PM_{2.5}$ and infertility in men and noise and infertility in women were present regardless of the degree of urbanisation, suggesting that the high mobility of our population did not affect the results. In Denmark, people of high socioeconomic status are more likely to live in urban areas than in more rural areas, and although infertility treatment is free of charge in Denmark, Danish couples with high education and high income are more likely to seek infertility treatment than couples with low education and low income.[56] One could also speculate that people in urban areas might have different healthcare seeking

behaviour than people in more rural areas. However, we observed comparable risk estimates for noise and air pollution among people with low, medium, and high educational level as well as among fourths of personal income, indicating that the results were not driven by socioeconomic differences in exposure levels or health seeking behaviour, or both.

Noise at the least exposed facade of a home is hypothesised to be a proxy for exposure to noise during nighttime sleep, as many people prefer their bedroom away from a busy street.[57] We observed that associations between this noise estimate and infertility across both men and women and age groups followed a linear association from 35 dB to around 45 dB, after which the association either levelled off or became negative. This makes it difficult to draw conclusions about the effects of noise at the least exposed facade on infertility. Therefore, to further explore whether noise at the least exposed facade had an impact on infertility risk, we investigated the effects of noise at the most exposed facade among people who had access to a "silent side," which we defined as having a facade with substantially lower levels of road traffic noise than at the most exposed facade, compared to people with no silent side. Interestingly, we found that hazard ratios for noise at the most exposed facade and infertility among women with a silent side were markedly lower than among people without a silent side. This suggests that having access to a more silent facade may protect against the stressful effects of noise.

Conclusions

Based on a nationwide cohort, designed to include a high proportion of people actively trying to achieve pregnancy, we found that $PM_{2.5}$ was associated with a higher risk of an infertility diagnosis among men and road traffic noise was associated with a higher risk of an infertility diagnosis among women older than 35 years, and possibly among men older than 37 years. As many western countries are facing declining birth rates and increasing maternal age at the birth of a first child, knowledge on environmental pollutants affecting fertility is crucial. If our results are confirmed in future studies, it suggests that political implementation of air pollution and noise mitigations may be important tools for improving birth rates in the western world.

Contributors: MS and AJ conceived and designed the study. MS, AHP, ORN, and AJ defined and generated the study population. AJ and BN defined the outcome. JK, MK, and JB developed the method for, and estimated, particulate air pollution. MS conducted the statistical analyses. MS and AJ drafted the manuscript, which was subsequently revised and approved by all authors. MS is the guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: The study is based on data from the Danish national registers, which belong to the Danish Ministry of Health and Statistics Denmark. The authors are thus not allowed to share them in their raw form.

Transparency: The lead author (MS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The involved research institutions will disseminate the study findings through press releases and patient organisations. Also, we plan to disseminate the results directly to national and international decision makers and officials within the area of environmental pollution.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: Additional tables S1-S7 and figures S1-S4