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The effect of current and future maternal exposure to near-surface ozone on preterm birth in 30 European countries—an EU-wide health impact assessment

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Abstract

Preterm birth is the largest contributor to neonatal mortality globally and it is also associated with several adverse health outcomes. Recent studies have found an association between maternal exposure to air pollution and an increased risk for preterm birth. As a constituent of air pollution, ozone is a highly reactive molecule with several negative health effects when present near earth's surface. This health impact assessment aims to estimate the proportion of preterm births—in current and future situations—attributable to maternal ozone exposure in 30 European countries (EU30). A literature search was performed using relevant keywords, followed by meta-analysis with STATA software in which five studies investigating exposure-response relationship of interest were included. The attributable proportion, and number of cases, was modelled with the software AirQ+ against current and future European ozone concentrations. According to our meta-analysis, the relative risk for giving birth preterm was calculated to 1.027 (95% CI 1.009–1.046) per 10 μg m^{-3} increase in ozone concentration. This rendered 7.1% (95% CI 2.5–11.7) of preterm births attributable to maternal ozone exposure to in EU30 during 2010, which is equal to approximately 27 900 cases. By 2050, the projected decrease in ozone precursor emissions rendered an estimated 30% decrease of ozone attributable preterm births. Not taking emission change into account, due to climate change the ozone-related preterm birth burden might slightly increase by 2050 in Central and Southern Europe, and decrease in Eastern and Northern Europe. In summation, these numbers make a substantial impact on public health.

1. Introduction

Preterm birth is commonly defined as birth before the gestational age of 37 weeks, and predisposes children several hazards with both immediate and future health. In 2015 alone, preterm birth caused globally approximately 1 million deaths before the age of 5 [1]. This equates to more than 2700 premature deaths daily, ranking complications emanating from preterm birth the largest contributor of neonatal death globally [2]; however, it is not only the alarming number of mortalities caused by preterm birth which pose a global threat to children's health. The infants that do survive will face an increased risk of a wide range of etiologies including cognitive, neurological, immunological, and gastrointestinal dysfunctions, along with chronic morbidities such as asthma and type two diabetes later in life [3–5]. Therefore, it is important to acknowledge that the hazardous consequences of prematurity are not necessarily limited to a defined time-period surrounding childhood, but may likewise affect an individual's health and life far into adult years [6].

Several risk factors surrounding preterm birth have previously been established, including facets of basic maternal lifestyle choices such as physical activity, diet, alcohol consumption, and tobacco use. The role of more complex contributors, such as genetics

and environmental factors, is less explored, albeit some associations have been suggested [3].

1.1. Air pollution and near-surface ozone

The World Health Organization (WHO) currently describes air pollution as the biggest environmental risk to health as the proportion of worlds' population living in areas where air pollutants exceed the safe levels, is estimated to 92% [7]. Several studies have recognized that air pollution has adverse effects on health by showing associations between air pollution exposure and morbidity, foremost of cardiovascular and respiratory etiology [8]. Air pollution—as mixture of various substances—include near-surface, sometimes called ground-level or tropospheric, ozone. Unlike several other air pollutants, near-surface ozone is not directly emitted, but rather photochemically formed in complex reactions when nitrogen oxide (NO_x) is exposed to sunlight in the presence of volatile organic compounds (VOCs) [9]. Hence, apart from the levels of precursor elements such as NO_x and VOCs, the rate of near-surface ozone formation is dependent on meteorological conditions such as the amount of sunlight, wind, and, most importantly, temperature on the surface [10]. As understood by a panoply of scientists, we will experience higher global temperatures with increased health effects in the future due to anthropogenic climate change [11]. As described by Doherty *et al* [12], many of the meteorological consequences of climate change, such as higher temperature, less cloud coverage, and less rainfall can synergistically contribute to an increase in near-surface ozone concentration, due to more efficient ozone formation and increases in natural emissions of VOCs. On the contrary, it should be noted that the emission of anthropogenic ozone precursors have decreased in all EU-member countries and are projected to decrease further in the future [13, 14].

In 2005, the EU has set a target value and WHO a guideline for the ozone concentration in ambient air for a daily 8 h maximum of 120 and 100 micrograms per cubic meter ($\mu g\ m^{-3}$), respectively [15]. However, a growing number of studies are finding adverse health effects from ozone exposures at even lower concentrations [16–20]. For instance, a study from the US by Bell *et al* [17] found associations between premature mortality and ozone exposures near typical background ozone levels at 20 $\mu g\ m^{-3}$, thus suggesting that there are almost no safe levels of near-surface ozone. For this reason, recommendations are starting to shift in regard to what cut-off value to use when assessing the health impacts of ozone. Amann *et al* [16] estimated earlier approximately 21 000 premature deaths were associated with ozone concentrations above 70 $\mu g\ m^{-3}$ in 25 European countries; however, with SOMO25 and inclusion of long-term effects, this estimation could rise to 55 000 [21]. As reviewed by Orru *et al* [22], different studies have applied different cut-off values and to reduce these divergencies, we have in this study chosen to adopt an ozone exposure cut-off at 50 $\mu g\ m^{-3}$ expressed as sum of means over 25 ppb (SOMO25). It is the yearly sum of the daily maximum of 8 h running average over 25 ppb.

A majority of the studies tackling the health effects of air pollution have traditionally focused on general mortality, or respiratory and vascular morbidity [23–25]. However, alternative endpoints such as cognitive development and reproductive health, have also been suggested [8]. Several studies have shown associations between ozone exposure, specifically, and negative birth outcomes [26–28]. The theories regarding the pathogenesis of ozone exposure are related to an ozone molecule's ability to promote free radical reactions in the body [29]. As free radicals come in contact with target molecules, they may become inactivated, initiating cellular damage through oxidation progressions referred to as oxidative stress [29]. It is suggested that oxidative stress, along with hemodynamics disruptions and inflammation in the mother, impairs the delivery of oxygen and nutrients to the foetus, thus causing a disturbed gestational process [30]. The increased levels of proinflammatory mediators resulting from oxidative stress can subsequently provoke, or increase, the risk for giving birth preterm [30–32]. This theory is supported by additional literature showing that systemic inflammation can trigger a preterm delivery [33]. A biological marker of inflammation in the body is the plasma level of C-reactive protein (CRP). In early pregnancy, exposure to certain air pollutants, ozone included, has been shown to increase CRP levels and then act as a potential trigger for preterm birth [34].

The existing knowledge regarding the extent of ozone related birth effects' is limited thus, to the best of our knowledge, this is the first continent-wide health impact assessment (HIA) quantifying maternal ozone exposure and the number of attributable cases of preterm birth. It aims to estimate the attributable proportion (AP) of preterm births that occur due to maternal ozone exposure during the first trimester of pregnancy. Moreover, we aim to quantify how ozone concentration due to changes in climate and emission levels change, and we estimate the AP for year 2050 in 30 European countries (EU30).

2. Materials and methods

2.1. HIA

A HIA utilizes a methodology for quantifying the health outcomes of a certain exposure [35]. The procedure follows a series of steps in which, firstly, an exposure-response function is selected—usually expressed as a relative risk. This exposure-response function is then applied to an outcome baseline to estimate the AP and number of cases caused by a certain exposure, e.g. near-surface ozone [36].

This methodology has been utilized by several other environmental health studies [37–39] and also by a similar study which investigated preterm birth as an outcome, but particulate matter as an exposure constituent [40].

2.2. Near-surface ozone modelling

First, to determine human exposure to near-surface ozone in Europe, the multi-scale atmospheric transport and chemistry (MATCH) model [41–43], that is Eulerian chemistry transport model (CTM) was applied at a 50 × 50 km horizontal resolution. The model used here includes ozone and particle forming chemistry considering ca 60 chemical species [44]. Meteorological 3D information is updated every hour in the model with an impact on concentrations in thermal- and photochemical reactions (e.g. temperature, cloud cover, solar radiation, humidity), transport, deposition and boundary layer processes (e.g. wind, temperature profile, precipitation, humidity, solar radiation), and the natural emissions of isoprene calculated online (e.g. temperature, solar radiation) following the Simpson *et al* [45] E-94 methodology, while terpene emissions are not treated in this model version. Isoprene chemistry is based on an adapted version of the Carter one-product mechanism [44, 46], while other gas-phase chemistry is based on the EMEP MSC-W EMChem09 scheme of Simpson *et al* [47] with reaction rate updates following the recommendations of International Union of Pure and Applied Chemistry (IUPAC) [41, 48]. The photolysis rates depend on photolytically active radiation, which is calculated from latitude, the time of day, and cloud cover. The dry deposition is modelled through a resistance approach. The dry deposition to stomata—modelled as described by Andersson and Engardt [49]—is dependent on soil moisture, temperature, solar radiation, and the humidity of the air. Thus, many processes in the model are impacted by climate change. MATCH is widely used for various air quality and, specifically, ozone research and operational services, such as daily European operational air quality forecasting [50] and national Swedish environmental surveillance (e.g. [51]) of ozone and deposition. The ozone performance of MATCH is commonly among the best in comparison with other European CTMs (e.g. [52]). The specific set up and evaluation of ozone were described in detail previously [13, 14, 21, 53, 54], but briefly recaptured here. Ozone concentrations from this set up were evaluated for the present situation compared to airbase measurement sites (see [54]), where MATCH had the lowest root mean square error of the four CTMs and a mean annual and summer bias of 1 ppb(v) and −1.1 ppb(v), respectively. MATCH was forced by the global climate model EC-EARTH and downscaled with the Rossby Climate regional climate model RCA4 [55]. They were both forced by the representative concentration pathway scenario RCP4.5 [56]. MATCH was also forced on the boundaries by the LMDz-INCA global model [57] and by anthropogenic air pollution precursor emissions of ECLIPSE v4a for the present (years 2005–2010) and the future (year 2050, current legislation). The evolution is considered coherent with the future evolution of the RCP4.5 scenario at 2050 [14].

In the current study the SOMO25 (the highest daily 8 h average exceeding 25 parts per billion (ppb) summarized from day 1 to 365) values have been applied. The population-weighted exposure (E_w) has been calculated by multiplying the SOMO25 concentration within each 50 × 50 km grid (E_i) by the number of individuals residing within the same grid (POP_i). The sum of the concentration of all grids was then divided by the total population of respective country (POP_{tot}) as: $\boldsymbol{E_w} = \frac{\mathbf{SUM}(\boldsymbol{E_i} \times \mathbf{POP_i})}{\mathbf{POP_{tot}}}$.

2.3. Preterm birth data

Secondly, the national baseline incidence rate of preterm birth for year 2010 in EU30 was obtained from the United Nations Statistics Division database [58], where data has been collected through examination of national and local administrative reporting registers, civil registration forms, and surveys. Data on current (2010) population size for each country in EU30 was likewise extracted from the WHO database [59] and for future (2050) populations Eurostat population projections [60].

2.4. Exposure-response function

To determine a pooled exposure-response function, a systematic literature review was conducted (figure 1). The scientific databases PubMed, CINAHL and Cochrane library were utilized in October 2017 using the terms 'Ozone' AND 'Preterm birth,' 'Ozone' AND 'Preterm delivery,' 'Air pollution' AND 'Premature birth.' Publications which met the inclusion criteria were exposure being ozone and outcome being preterm birth, which were screened through an abstract and full text review. Between the 14 examined studies [61–74], significant divergencies in exposure variables were observed. The most fundamental differences were differences in the exposure period, either first trimester, third trimester or whole pregnancy, and the type of ozone exposure value (1 h, 8 h and 24 h maximum). Therefore, a second set of inclusion criteria was employed. Studies assessing first trimester ozone exposure were measured at an 8 h maximum due to the larger number of studied phenomena and more profound effects with either first or third trimester exposure data, thus leaving five studies [63, 64, 69, 71, 74] (figures 1 and 2).

2.5. Meta-analysis

The meta-analysis of the five studies was done in the statistical software environment of *STATA 13* using the '*metan*' package [75]. The software designated a

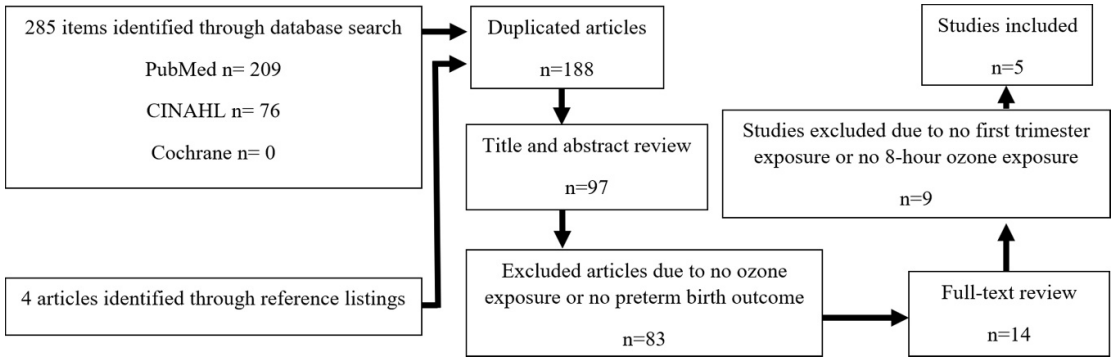

Figure 1. Flowchart illustrating process of literature search and selection.

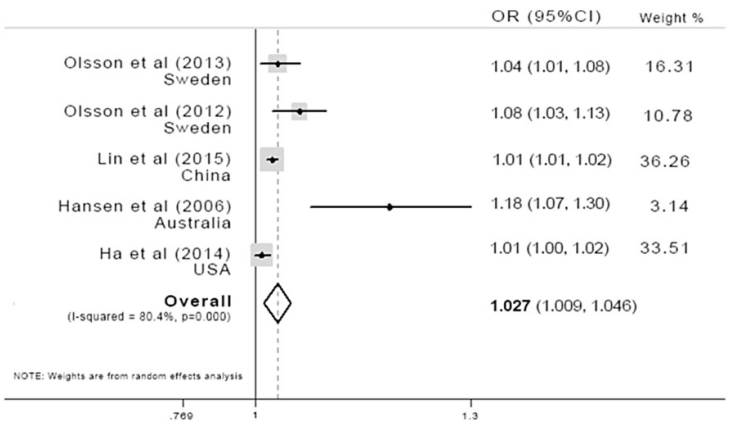

Figure 2. Pooled effect size estimates presented in a forest plot. OR represents study-specific and overall odds ratios (OR). Weight represents the percentage of weight each study [63, 64, 69, 71, 74] has been assigned in the overall calculation thus indicating the influence on the overall effect size.

certain impact on the overall effect size depending on the level of uncertainty in each study. This meant that the wider confidence interval a certain study carried, the less influence it would have over the overall effect size (figure 2). All studies, which did not present an effect size per 10 μg m^{-3} increase in ozone concentration, were recalculated accordingly. The meta-analysis effect model used was the DerSimonian and Laird mixed-effect (random effect) model [76, 77] (supplementary material (available online at stacks.iop.org/ERL/16/055005/mmedia)).

2.6. Calculation of attributable effects

To estimate the proportion and number of preterm births caused by maternal ozone exposure in Europe, the exposure-response function was applied to the ozone levels in each respective country. The AP and number of cases were calculated using the WHO developed software *AirQ+*. This WHO developed software can be used to quantify health effects of certain air pollutants, including ozone. The estimated impact is grounded on a log-linear relationship between relative risk (RR) and concentration levels.

The AP is then estimated as defined: $\mathbf{AP} = \mathbf{\Sigma}\left[\mathbf{RR}\left(\mathbf{c}\right) - \mathbf{1}\right] \times \mathbf{p}\left(\mathbf{c}\right) / \mathbf{\Sigma}\left[\mathbf{RR}\left(\mathbf{c}\right) \times \mathbf{p}\left(\mathbf{c}\right)\right]$, where p(c) is the proportion of the population.

To generate an estimate of the excess number of cases of preterm birth attributable to ozone exposure (ΔY), the software uses the baseline preterm birth rate (Y_0) and the population at risk (pop), defined as: $\boldsymbol{\Delta Y} = \left(\boldsymbol{Y_0} \times \mathbf{pop}\right) \times \left(\mathbf{exp}^{\boldsymbol{\beta} \times \boldsymbol{\Delta X}}\right)$, where β represents the effect size and ΔX is the variation in concentration.

3. Results

3.1. Ozone levels

The current population average SOMO25 level for EU30 was 10 172 μg m^{-3}·d, ranging from 6667 to 18 230 μg m^{-3}·d (figure 3). The highest SOMO25 values were recorded in the Mediterranean region with Malta, Cyprus, Greece, Italy, and Portugal being the five highest exposed countries with a combined SOMO25 average value of 15 351 μg m^{-3}·d, that would mean around 92 μg m^{-3} as daily 8 h max mean. The lowest levels were found in the United Kingdom, Finland, and the Baltic States due to low levels during winter period, around 50 μg m^{-3} as daily 8 h max mean. The average SOMO25 level for the least exposed countries was 6847 μg m^{-3}·d.

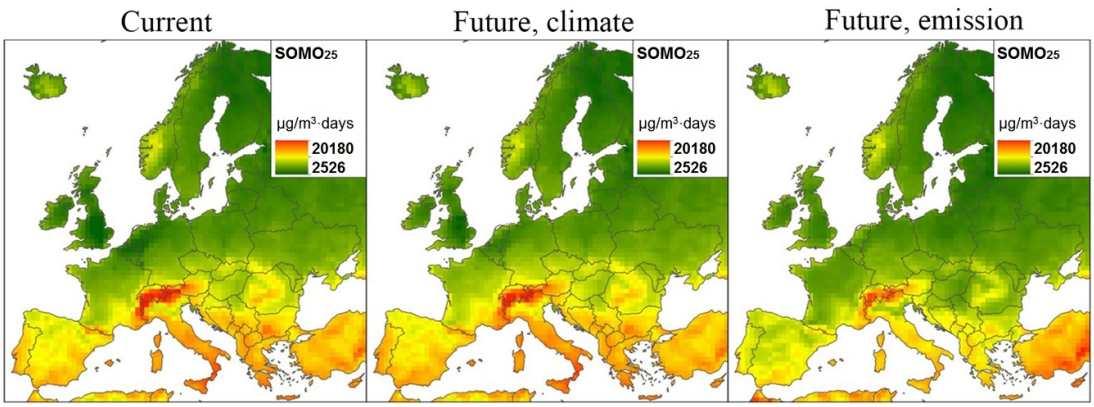

Figure 3. Ozone SOMO25 (sum of ozone means over 25 ppb) levels for current (2005–2010) and future (2050) driven by climate (middle) and climate and emission (right) changes.

In 2050, the overall ozone concentrations based on climate change were projected to be left relatively unchanged when compared to the current EU30 average (an average increase with 0.3%). However, some individual countries saw more tangible climate effects in the form of both increases and decreases. Changes in SOMO25 values due to an altered climate yielded an increase in Central-Europe (e.g. in Luxembourg 12% increase in SOMO25 levels) to a 6%–7% decrease in the Baltic States (Estonia, Latvia and Lithuania).

In the future emissions-based model, all EU30 countries presented significant reductions which in all cases were greater than reductions driven by climate change. The MATCH estimation for future SOMO25 levels based on changes in ozone precursor emissions yielded an EU30 average reduction of 29%, ranging from a SOMO25 decrease by 14% for Cyprus to a 38% reduction for Hungary.

3.2. Pooled ozone effect size estimates from meta-analysis

The studies used for the modelling of an exposure-response function [63, 64, 69, 71, 74] had a sample size range from approximately 28 000 to 1.5 million subjects. The mean daily 8 h maximum ozone concentration, as short-term exposure, varied in studies between 53.1 and 84.5 μg m^{-3}. The studies adjusted for a varying set of possible confounders such as age, smoking, parity, co-morbidity, the season of conception, and co-pollutants effects. All studies used similar methodologies for pollutant measurements and statistical analysis, and all used the same maternal exposure window, which was average exposure during the first trimester. The increased risk for giving birth preterm based on ozone exposure were expressed as odds ratios and ranged from 1.01 to 1.18 (95% CI 1.00–1.30) per 10 μg m^{-3} increase in ozone concentration. When weighted and modelled, the respective effect sizes generated a pooled effect size of 1.027 (95% CI 1.009–1.046) per 10 μg m^{-3} increase in the mean daily 8 h maximum ozone concentration (figure 2).

3.3. Number of current preterm births due to near-surface ozone exposure in 2010

The average population proportion attributable to preterm birth caused by ozone was estimated to 7.2% (95% CI 2.5–11.8) (table 1). The largest attributable proportions were found in countries with higher SOMO25 values, i.e. the Mediterranean region where Malta, Cyprus, and Greece had an estimated AP of 12.5% (4.4–20.2), 10.7% (3.7–17.4), and 10.4% (3.6–17.0), respectively. The smallest AP was found in the northern parts of Europe, where SOMO25 values were the lowest. The United Kingdom, Finland, and Lithuania showed an estimated AP of 4.7% (1.6–7.7), 5.1% (1.7–8.4) and 5.2% (1.8–8.7), respectively.

In absolute numbers, more preterm births attributable to ozone were found in countries with larger populations, e.g. France reported the highest total number of attributable preterm births (3889, 95% CI 1353–6340) related to maternal ozone exposure. Conversely, due to its small population, Iceland, who also experienced a relatively small attributable proportion, presented the smallest number of attributable cases: 20 (95% CI 7–34) preterm births attributable to maternal ozone exposure. The total number of attributable cases in EU30 in 2010 was estimated to be 27 871 (95% CI 9611–45 854) premature births.

3.4. Future estimates of preterm births due to near-surface ozone exposure and populations change in 2050

Climate change will only slightly alter the attributable impact, which relates to the moderate changes in SOMO25 values in the same model. If population baseline rates remain unchanged, we expect altogether 424 more cases of preterm birth in EU30. In this analysis, the EU30 average near-surface ozone induced AP of preterm birth is expected to decrease

Table 1. EU30 attributable proportion (AP, %), attributable number of cases (*N*) with 95% confidence interval (95% CI) due to near-surface ozone exposure (under SOMO25 values) currently (2005–2010) and in the future (2050), taking climate and emissions change into account.

	Current		Future							
			Climate change		Emissions change		Populations change		Changes combined	
Country	AP% (95% CI)	N (95% CI)	AP% (95% CI)	N (95% CI)	AP% (95% CI)	N (95% CI)	AP% (95% CI)	N (95% CI)	AP% (95% CI)	N (95% CI)
Austria	8.5 (2.9–14.0)	738 (255–1209)	8.5 (2.9–13.9)	733 (254–1200)	5.8 (2.0–9.7)	507 (174–838)	8.5 (2.9–14.0)	799 (276–1309)	5.8 (2–9.6)	545 (188–901)
Belgium	4.6 (1.6–7.7)	470 (161–781)	5.1 (1.7–8.4)	514 (176–852)	3.8 (1.3–6.4)	390 (133–650)	4.6 (1.6–7.7)	531 (182–882)	4.2 (1.4–7)	482 (164–801)
Bulgaria	9.3 (3.2–15.1)	560 (194–915)	9.1 (3.2–14.9)	551 (191–901)	6.0 (2.0–9.9)	360 (124–595)	9.3 (3.2–15.1)	645 (223–1054)	5.9 (2–9.8)	408 (141–675)
Switzerland	9.3 (3.2–15.2)	520 (181–850)	9.3 (3.2–15.2)	521 (181–852)	6.5 (2.2–10.8)	366 (126–604)	9.3 (3.2–15.2)	672 (234–1099)	6.5 (2.2–10.8)	474 (163–783)
Czech Republic	6.7 (2.3–11.1)	550 (189–907)	6.8 (2.3–11.1)	554 (191–914)	4.6 (1.6–7.6)	375 (128–623)	6.7 (2.3–11.1)	556 (191–917)	4.7 (1.6–7.6)	382 (131–635)
Cyprus	10.7 (3.7–17.4)	157 (55–256)	10.5 (3.7–17.1)	154 (54–251)	9.1 (3.2–14.9)	134 (47–219)	10.7 (3.7–17.4)	127 (45–207)	8.9 (3.2–14.6)	107 (37–174)
Germany	5.7 (2.0–9.5)	3518 (1206–5821)	6.0 (2.1–10.0)	3690 (1267–6099)	4.2 (1.4–7.0)	2586 (882–4301)	5.7 (2.0–9.5)	3401 (1166–5627)	4.4 (1.5–7.4)	2622 (896–4356)
Denmark	5.6 (1.9–9.3)	249 (85–412)	5.5 (1.9–9.2)	245 (84–406)	4.1 (1.4–6.8)	182 (62–302)	5.6 (1.9–9.3)	283 (97–468)	4 (1.4–6.7)	203 (70–338)
Estonia	5.5 (1.9–9.1)	52 (17–86)	5.2 (1.8–8.6)	49 (17–82)	3.8 (1.3–6.3)	36 (12–59)	5.5 (1.9–9.1)	45 (15–75)	3.6 (1.2–0.1)	29 (10–49)
Spain	8.9 (3.1–14.5)	2988 (1036–4888)	9.0 (3.1–14.8)	3034 (1053–4961)	6.2 (2.1–10.2)	2079 (714–3435)	8.9 (3.1–14.5)	2952 (1023–4829)	6.3 (2.1–10.4)	2086 (717–3444)
Finland	5.1 (1.7–8.4)	185 (63–306)	4.8 (1.6–7.9)	174 (60–289)	3.6 (1.2–6.0)	131 (44–218)	5.1 (1.7–8.4)	189 (64–313)	3.4 (1.1–5.6)	126 (43–211)
France	6.8 (2.4–11.3)	3817 (1314–6291)	7.2 (2.5–11.8)	4001 (1379–6586)	4.7 (1.6–7.8)	2605 (890–4326)	6.8 (2.4–11.3)	4159 (1432–6855)	5 (1.7–8.1)	2975 (1018–4935)
Greece	10.4 (3.6–17.0)	803 (280–1306)	10.4 (3.6–16.8)	797 (278–1297)	7.2 (2.5–11.8)	553 (191–910)	10.4 (3.6–17.0)	648 (226–1055)	7.2 (2.5–11.7)	443 (153–730)
Hungary	7.2 (2.5–11.8)	583 (201–959)	7.1 (2.4–11.6)	574 (198–946)	4.4 (1.5–7.4)	361 (123–600)	7.2 (2.5–11.8)	496 (171–816)	4.3 (1.4–7.3)	303 (103–504)
Ireland	5.6 (1.9–9.2)	247 (85–409)	5.5 (1.9–9.1)	245 (84–405)	4.2 (1.4–7.0)	185 (36–308)	5.6 (1.9–9.2)	296 (102–490)	4.1 (1.4–6.9)	220 (43–365)
Iceland	6.0 (2.0–9.8)	20 (7–34)	5.7 (2.0–9.4)	20 (7–32)	4.6 (1.5–7.7)	16 (5–26)	6.0 (2.0–9.8)	23 (8–39)	4.4 (1.5–7.4)	18 (6–28)
Italy	9.9 (3.4–16.1)	3889 (1353–6340)	9.9 (3.5–16.2)	3905 (1359–6365)	6.8 (2.3–11.2)	2673 (920–4406)	9.9 (3.4–16.1)	3527 (1227–5750)	6.8 (2.4–11.3)	2434 (838–4012)
Lithuania	5.2 (1.8–8.7)	112 (38–185)	4.9 (1.7–8.1)	104 (36–173)	3.5 (1.2–5.8)	74 (25–124)	5.2 (1.8–8.7)	73 (25–121)	3.3 (1.1–5.4)	45 (16–76)
Luxembourg	4.9 (1.7–8.3)	23 (8–38)	5.5 (1.9–9.1)	26 (9–43)	4.2 (1.4–7.0)	20 (7–33)	4.9 (1.7–8.3)	36 (13–60)	4.7 (1.6–7.7)	36 (12–59)
Latvia	5.2 (1.8–8.7)	50 (17–83)	4.9 (1.7–8.1)	47 (16–78)	3.5 (1.2–5.8)	33 (11–56)	5.2 (1.8–8.7)	33 (11–55)	3.3 (1.1–5.4)	21 (7–35)
Malta	12.5 (4.4–20.2)	30 (11–49)	12.5 (4.4–20.1)	30 (11–48)	9.0 (3.1–14.8)	22 (8–35)	12.5 (4.4–20.2)	32 (12–52)	9 (3.1–6.7)	23 (8–36)
Netherlands	5.0 (1.7–8.3)	733 (251–1216)	5.3 (1.8–8.8)	779 (267–1291)	4.3 (1.5–7.1)	628 (214–1045)	5.0 (1.7–8.3)	752 (257–1247)	4.6 (1.6–17.2)	684 (233–1138)
Norway	6.0 (2.10.0)	222 (76–367)	5.8 (2.0–9.5)	212 (73–351)	4.5 (1.5–7.5)	167 (57–277)	6.0 (2.10.0)	302 (103–499)	4.4 (1.4–6.6)	217 (74–360)
Poland	5.8 (2.0–9.7)	1689 (579–2793)	5.6 (1.9–9.3)	1630 (559–2699)	3.9 (1.3–6.5)	1130 (385–1881)	5.8 (2.0–9.7)	1474 (505–2438)	3.8 (1.2–6.2)	952 (324–1587)
Portugal	9.5 (3.3–15.4)	767 (266–1251)	9.8 (3.4–15.9)	790 (275–1289)	6.4 (2.2–10.6)	519 (179–857)	9.5 (3.3–15.4)	687 (238–1120)	6.6 (2.3–10.9)	479 (166–791)
Romania	8.0 (2.8–13.1)	1186 (410–1947)	7.8 (2.7–12.8)	1162 (401–1909)	5.1 (1.7–8.4)	755 (258–1252)	8.0 (2.8–13.1)	910 (315–1494)	5 (1.6–8.2)	568 (194–942)
Sweden	5.6 (1.9–9.3)	388 (133–643)	5.4 (1.8–8.9)	373 (128–618)	4.0 (1.4–6.7)	279 (95–464)	5.6 (1.9–9.3)	479 (164–794)	3.9 (1.3–6.4)	331 (113–551)
Slovenia	9.1 (3.2–14.9)	158 (55–259)	9.1 (3.2–14.9)	158 (55–258)	6.2 (2.1–10.2)	107 (37–176)	9.1 (3.2–14.9)	152 (53–250)	6.2 (2.1–10.2)	103 (36–169)
Slovakia	7.3 (2.5–12.1)	266 (92–438)	7.2 (2.5–11.9)	261 (90–430)	4.8 (1.6–7.9)	173 (59–288)	7.3 (2.5–12.1)	244 (84–401)	4.7 (1.6–7.8)	155 (53–259)
United Kingdom	4.7 (1.6–7.7)	2901 (991–4818)	4.7 (1.6–7.9)	2959 (1011–4914)	3.9 (1.3–6.5)	2432 (829–4049)	4.7 (1.6–7.7)	3477 (1188–5774)	3.9 (1.3–6.7)	2973 (1014–4949)
EU-30	7.2 (2.5–11.8)	27 871 (9611–45 854)	7.1 (2.5–11.7)	28 295 (9761–46 538)	5.1 (1.7–8 .4)	19 876 (6801–32 960)	7.2 (2.5–11.8)	28 078 (9681–46 198)	5 (1.7–8.3)	20 328 (6936–33 696)

from 7.1% to 5.1%, as a consequence of reduced emissions. Subsequently, as the EU population is expected to increase, the effects on preterm birth could increase in total by 1%, whereas the effects decrease a third in Latvia and Lithuania and increase by more than 50% in Luxembourg. Seen over the whole EU30 region and all three factors together, the total number of attributable preterm births in 2050 is expected to be 7543 fewer than in 2010 (table 1).

4. Discussion

This multinational study evaluates the attributable effects of maternal near-surface ozone exposure on preterm birth. From the meta-analysis—which included five studies concerning maternal ozone exposure during the first trimester and the subsequent risk for preterm birth—we estimate the increased risk for preterm birth to be 2.7% per 10 μg m^{-3} increase in near-surface ozone concentration. This generated a current average AP of 7.2%, or approximately 27 900 preterm births caused by maternal ozone exposure. Should future ozone concentration adhere to the air pollution emissions, climate scenarios, and population projections used here, nearly 27% fewer preterm births are to be expected in 2050. It is, however, important to acknowledge that the potential effect on the European preterm birth incidence rate is only due to maternal ozone exposure. There are many factors that impact the preterm birth incidence rate in a chosen setting, but none other than maternal ozone exposure is investigated here. Each of these results will be discussed and elaborated upon below.

Firstly, the result from the meta-analysis (the increased RR for preterm birth 1.027 per 10 μg m^{-3} increase in ozone exposure during first trimester) can be compared with corresponding studies, where other ozone exposure windows have been used. These studies have yielded RRs between 1.02 and 1.05 [66, 67, 72], which is similar to our results. The elevated risk for preterm birth may also be compared with the risks of exposures to $PM_{2.5}$. In a meta-analysis comprised from 13 studies, Sun *et al* [78] estimated the elevated risk for preterm birth caused for every 10 μg m^{-3} increase in $PM_{2.5}$ concentration during the entire pregnancy to be 13%; however, extensive heterogeneity between the included studies rendered a rather high level of uncertainty in the study. They applied exposure-response function from Sun *et al* [78] meta-analysis that included only studies fully adjusted for other covariates and pollutants.

Although a majority of studies have found positive associations between air pollution and preterm birth, some studies have found no or negative associations [79, 80]. Likewise, some studies have not been able to establish significant associations between maternal ozone exposure, specifically, and the risk for preterm birth [62, 70, 73]. Stieb *et al* [80] have discussed that part of this inconsistency may be explained by the heterogenic methodologies between studies as both outcomes and pollutants varied widely, and often multi-pollutant models were utilized. Another complicating factor is that in almost half of the cases of preterm birth, the underlying cause remains unidentified [81], making it reasonable to assume that the driving force behind preterm birth mostly will occur as a result of several interacting factors with varying impact capacity [2]. Moreover, the pathophysiology on how ozone affects the gestational environment surrounding the foetus is not yet fully understood. The mechanism by which preterm birth could be triggered by air pollutants is believed to be related to oxidative stress and inflammation, which in turn would disrupt the delicate processes surrounding gestation [32]. Still, a growing body of scholarship currently focuses on establishing associations for exposure to critical air pollutants in general [1, 82–85] and for ozone exposure in particular [26, 61, 67, 70, 72].

Secondly, we have applied the SOMO25 concept (yearly sum of the daily maximum of 8 h running average over 25 ppb) in our HIA, whereas epidemiological studies have applied actual concentrations (ppb, μg m^{-3}). The rationale behind this is that SOMO is a summary estimate—it helps to reduce the uncertainties of the concentration—response function at very low concentrations as its linearity does not extend down to zero and it reflects seasonal cycle, e.g. very low levels at winter and with-out SOMO we would underestimate the effects [8, 86, 87]. When we accounted for impacts from a cut-off of 50 μg m^{-3} (SOMO25), the excess risk caused by maternal near-surface ozone exposure yielded an estimated average 7.2% AP of preterm birth in EU30 in 2010. These results can be interpreted as out of 100 preterm births, seven are (in combination with other risk factors) the consequence of a maternal exposure to ozone during the first trimester of pregnancy. Accumulated across the studied European countries, the attributable number of cases due to near-surface ozone is estimated currently to be approximately 27 900 preterm births. This can be compared to a similar study conducted by Malley *et al* [40] that investigated the global AP of preterm birth caused during the entire pregnancy $PM_{2.5}$ exposure over 10 μg m^{-3}. In this study, it was estimated that in Europe, 34 800 preterm births were due to fine particles exposure. The applied exposure-response function was based on a meta-analysis that included only studies fully adjusted for other covariates and pollutants [78], thus we cannot expect overlapping effects with ozone.

Our HIA has applied ozone concentrations exceeding ~50 μg m^{-3} (SOMO25) when estimating the impact of ozone on preterm birth. This cut-off is, to some degree, lower compared to previous HIAs which adopted concentrations over ~70 μg m^{-3} (SOMO35) [16, 88, 89]. The rationale behind using

SOMO25 as a concentration cut-off is based on the earlier mentioned indications that suggest health effects occur in low ozone concentrations, such as typical background values [17–20]. A similar cut-off was also applied in a recent EU-wide ozone-related mortality impact assessment [21]. Also, in three of the five studies included into our meta-analysis, the ozone levels were close to SOMO25 levels [64, 71, 74]. If the ∼70 μg m^{-3} (SOMO35) cut-off would have been used, the effect-estimate would be more than two times lower (supplementary material). The difference is especially large if we compare the 'future emissions' scenarios as the levels are expected to be mostly below 70 μg m^{-3}. With SOMO35, only a little more than 4000 preterm births are expected with future emissions. This would probably underestimate the real effects based on current susceptibility [17–20].

Another variable in exposure variation is the estimation of averaging time of exposure, as 1 h or 8 h max or 24 h average. Since ground-level ozone formation is dependent on sunlight, the concentration levels vary substantially over the course of the day, and exposure values are therefore affected considerably by what estimation technique is used [90]. We have applied an 8 h maximum as recommended by WHO [8]. Moreover, the same assigned exposure could result in different outcomes depending on how much time a particular individual spends outdoors, under that exposure, thus affecting the actual dose of ozone. The country-based exposures, in the future projections in this study, are based on climate and emission models that utilize a 50 × 50 km horizontal resolution. From a continental and country-wide perspective, this resolution can be regarded as high, but on an individual level, it must be seen as rather crude. This introduce a risk of exposure misclassification. For the same reason, ozone exposure is likely overestimated in those areas close to high emission areas, and likewise underestimated in suburban locations, where local emissions could affect the near-surface ozone levels [13].

Thirdly, when including the attributable effects for future air pollution emission levels in EU30, the estimated number of preterm births in 2050 was reduced by 30% when compared to 2010. This is equals to almost 8000 less cases of preterm birth in 2050, meaning that almost one third of all preterm births attributable to ozone exposure could be avoided if ozone precursor emissions follow the predicted emission scenarios. The leading cause behind these drops is the improved technique for reducing vehicular exhaust emissions—e.g. the development of three-way catalytic converters—and legislation regarding ozone precursor emissions [91]. Nevertheless, several uncertainties are related to ozone modelling itself. In our analysis we have applied emission data from the periods of 2005–2010 and 2050 and climate data from the periods of 1991–2000 and 2046–2055. If the future period is centred around 2050, the current climate data is from earlier period than 2010. This might have made bias due to climate change in the last decade [92]. It is also important to note that this estimation does not consider changes in the preterm birth or birth rate as there are no projections on future rates for 2050. During the period of 2010 and 2015 there has been increase of preterm births in some countries and decrease in others [93], but this information does not allow us to make long-term projections. If the preterm birth incidence or birth rate increases/decreases in EU30, the change of attributable cases is misestimated.

Fourthly, when we modelled and projected for changes in the climate, ozone concentration levels for 2050 were found to be relatively similar to those of year 2010, thus leaving the attributable effects relatively unchanged (a 1.6% increased AP in the climate model was seen). The minor impact of ozone exposure in the climate model stems from the fact that the European ozone concentrations did not increase substantially in the current future projections. The highest increase in ozone concentration, due to climate change, was found in Luxembourg, where SOMO25 rose by 12.9% in 2050. If we would calculate the factual daily exposure for this increase, it is equal to a 2.4 μg m^{-3} daily increase, which partly can explain the very small effects seen in the climate model.

Apart from the limitations already discussed, this study unavoidably also inherits restrictions from the original studies from which the current exposure-response coefficient has been calculated. All studies in the meta-analysis [63, 64, 69, 71, 74] share the risk of exposure misclassification, as individual exposures are assigned based on ozone concentrations registered by local measurement stations, typically located at rooftop level throughout the city. As previous research, and earlier discussion has indicated [94], this does not, necessarily, reflect the true individual exposure as other meaningful exposure factors, such as time spent outdoors and commute distance, are not taken into account.

When interpreting these findings, one must also consider an excessive degree of uncertainty. Ultimately, it is the exposure-response function which yields the final results of this study, but within the exposure-response function there are factors with varying underlying degrees of uncertainty. The effect size is, for instance, expressed as a relative risk with a 95% confidence interval ranging from 1.009 to 1.046, which puts the average estimate of 27 871 preterm births to be between 9611 and 45 854 cases. Another crucial factor for the function, and subsequently the results, is near-surface ozone concentration. First, we have used 1991–2000 climate data together with 2005–2010 emission data, which may have biased the estimated concentrations. Moreover,

air pollutant emissions are affected by uncertainties in emission factors, which are largely related to real-life end-of-pipe emission control and actual activity data. As show by Lin *et al* [95] the errors for air pollution emissions could range from 10% to 170% depending on the pollutant and region; however, air pollution emissions are relatively smaller for Western Europe. Many uncertainties are also related to ozone modelling, itself, and atmospheric chemical and physical processes such as dry deposition, wet scavenging, ozone precursors transport, and ozone formation [96, 97]. According to Derwent *et al* [98], the uncertainties from ozone sources and sinks are larger than in model formulation.

Second, there are a multitude of factors impacting the concentration of ozone in the future. Factors impacting the possible future exposure of individuals to ozone in Europe include the pathway for ozone precursor emissions, climate change and the greenhouse gas emission scenario, and sensitivities and parameterizations of the specific climate models and CTMs used to describe the future evolution. There is inherent uncertainty in what path the future ozone exposure evolution will take. The air pollution emission scenarios projected in this project depend on policy makers decisions and the technical solutions available; there are other possible future evolutions.

Watson *et al* [14] compared the impact of climate change, under Current Legislation Emissions (CLE) scenario, and maximally technically feasible reductions emissions modelled by four CTMs. Langner *et al* [44] compared emission change to the impact of climate change on ozone concentrations in two global climate model simulations. Colette *et al* [99] compared a number of different CTM model sensitivities to climate change scenarios. All these studies show that, for a great fraction of the European population, the main contributing factor in ozone concentrations is the pathway of anthropogenic ozone precursor emissions. Thus, future health impacts will be highly dependent on measures taken, and these measures need to be introduced across the northern hemisphere, not only in Europe. Climate change is projected to lead to higher ozone exposure, a so-called climate penalty. Measures to reduce climate change would also act to reduce ozone exposure in most parts of Europe, but the most effective measure is to reduce anthropogenic precursor emissions.

This assessment has focused on the effects of near-surface ozone exposure on preterm birth in the European region exclusively. It should be recognized that the world-wide attributable number of cases of preterm births due to maternal ozone exposure would be substantially higher. This is not only due to the inclusion of larger populations, but in low-income settings, a combination of megacities, poor ozone precursor emission regulations, and a hot climate with a lot of sunlight will produce ozone levels which are considerably higher than those found in Europe. An example of this can be found in Latin America, as Sao Paolo, Brazil can experience several days during summer where ambient ozone concentrations may exceed 400 μg m^{-3} [100], whereas European levels during the summer typically exceed 200 μg m^{-3} and are less than 300 μg m^{-3}, even in extreme summers, like the one experienced in 2003 [101]. This highlights the essentiality of strict global emission legislation, whose need is most pressing in low-income settings, where current regulations in many cases are insufficient.

5. Conclusion

Air pollution is considered the largest environmental threat to human health. Near-surface ozone has been shown to have numerous adverse health effects including facets of reproductive health. According to our meta-analysis, for each 10 μg m^{-3} increase in maternal first trimester ozone exposure concentration, the risk for preterm delivery will increase by 2.7%. Subsequently, for 30 European countries, the population AP of preterm births due to first trimester maternal ozone exposure was estimated currently to 7.2%. This proportion equals to a number of 27 871 babies born prematurely in 2010.

Highlighting the importance of emission control and stern legislation regarding ozone precursor emissions, this assessment likewise found that in 2050, with consideration of population change, an estimated number of around 7500 preterm births will be avoided as a result of reduced ozone precursor emissions. Not taking emission and population change into account, due to climate change the ozone-related preterm birth burden might slightly increase by 2050 in Central and Southern Europe, and decrease in Eastern and Northern Europe.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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Author contributions

JE conceived the study; JE, BF, and HO designed the research; JE and DO performed the meta analyses; HO made maps; JE and HO made the health impact calculations; CA modelled the near-surface ozone and all authors wrote the paper.

Conflict of interest

The authors declare no conflict of interest.

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