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Mortality attributable to ambient fine particulate matter and nitrogen dioxide in Switzerland in 2019: Use of two-pollutant effect estimates

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ABSTRACT

Introduction: Air pollution health risk assessments have traditionally used single-pollutant effect estimates for one proxy ambient air pollutant such as $PM_{2.5}$. Two-pollutant effect estimates, i.e. adjusted for another correlated pollutant, theoretically enable the aggregation of pollutant-specific health effects minimizing double-counting. Our study aimed at estimating the adult mortality in Switzerland in 2019 attributable to $PM_{2.5}$ from a single-pollutant effect estimate and to the sum of $PM_{2.5}$ and NO_2 from two-pollutant estimates; comparing the results with those from alternative global, European and Swiss effect estimates.

Methods: For the single-pollutant approach, we used a $PM_{2.5}$ summary estimate of European cohorts from the project ELAPSE, recommended by the European Respiratory Society and International Society for Environmental Epidemiology (ERS-ISEE). To derive the two-pollutant effect estimates, we applied ELAPSE-based conversion factors to ERS-ISEE $PM_{2.5}$ and NO_2 single-pollutant effect estimates. Additionally, we used World Health Organization 2021 Air Quality Guidelines as counterfactual scenario, exposure model data from 2019 and Swiss lifetables.

Results: The single-pollutant effect estimate for $PM_{2.5}$ (1.118 [1.060; 1.179] per 10 $\mu g/m^3$) resulted in 2240 deaths (21,593 years of life lost). Using our derived two-pollutant effect estimates (1.023 [1.012; 1.035] per 10 $\mu g/m^3$ $PM_{2.5}$ adjusted for NO_2 and 1.040 [1.023; 1.058] per 10 $\mu g/m^3$ NO_2 adjusted for $PM_{2.5}$), we found 1977 deaths (19,071 years of life lost) attributable to $PM_{2.5}$ and NO_2 together (23% from $PM_{2.5}$). Deaths using alternative effect estimates ranged from 1042 to 5059.

Discussion: Estimated premature mortality attributable to $PM_{2.5}$ alone was higher than to both $PM_{2.5}$ and NO_2 combined. Furthermore, the proportion of deaths from $PM_{2.5}$ was lower than from NO_2 in the two-pollutant approach. These seemingly paradoxical results, also found in some alternative estimates, are due to statistical imprecisions of underlying correction methods. Therefore, using two-pollutant effect estimates can lead to interpretation challenges in terms of causality.

1. Introduction

Air pollution health risk assessments (AP-HRAs) provide a methodology to quantify health effects attributable to exposure to ambient air pollution in entire populations (WHO 2016b). The following four main input data are used in AP-HRAs: a) population exposure to pollution, b) counterfactual scenario (i.e. the minimum concentration from where the health burden is quantified), c) concentration-response function expressed as an effect estimate per an increment in concentration and d) baseline health data (i.e. incidence in the area of study) (Castro et al., 2022).

Effect estimates are key input data in AP-HRAs and can be classified as single-pollutant (without adjustment for other pollutant) or two-pollutant (both mutually adjusted) depending on the number of pollutants involved. To date, many studies quantifying deaths attributable to air pollution used a proxy pollutant such as particulate matter with a diameter of 2.5 μm or smaller ($PM_{2.5}$) to quantify the burden of air pollution (e.g. ETC/ACM 2016; Khomenko et al., 2021; Murray et al.,

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2020; WHO, 2016a). $PM_{2.5}$ is a mixture of solid and liquid air pollutant components and has one of the largest evidence bases for health effects compared with other air pollutants (US EPA, 2019). This makes $PM_{2.5}$ an appropriate indicator of long-term exposure to air pollution in AP-HRAs. Although it is well established that air pollutants other than $PM_{2.5}$ have also health effects, summing up the burden for various pollutants would result in partial double counting, if they are correlated and the traditional single-pollutant effect estimates are used, i.e. if study results are not mutually adjusted for them (WHO 2013). To account for effects from pollutants other than $PM_{2.5}$, some international AP-HRAs (e.g. ETC/ACM 2016; Khomenko et al., 2021) have considered two indicators of long-term exposure to air pollution: $PM_{2.5}$ and nitrogen dioxide (NO_2). However, the resulting mortality burden was presented separately and not directly added to prevent from the above mentioned double-counting.

Two-pollutant effect estimates are considered to show the effect of one pollutant independent from a second by adjusting for the effect of the latter pollutant in the statistical analysis. Therefore, two-pollutant effect estimates, in theory, may enable the quantification of the mortality attributable to each air pollutant separately, while minimizing the risk of double-counting of health effects. The WHO project HRAPIE, which provided recommendations on the use of effect estimates for AP-HRAs in 2013, already highlighted these benefits (WHO 2013). This is particularly useful in a context where burden of air pollution is related to specific air pollution sources, like in assessments of transport externalities (ARE, 2014). On the other hand, it was also acknowledged that two-pollutant effect estimates involve risks of bias for one of the two pollutants, in case of exposure measurement errors and high underlying correlations producing variance inflation (WHO 2013). Two-pollutant effect estimates have thus been rarely used in AP-HRAs. The work of the British Committee on the Medical Effects of Air Pollutants (COMEAP) is an exception, adding health effects of $PM_{2.5}$ and NO_2 with two-pollutant effect estimates (COMEAP, 2018; Gowers et al., 2020).

The choice of the appropriate effect estimate among new available single- and two-pollutant effect estimates is challenging. In 2013, the WHO project HRAPIE recommended using the single-pollutant effect estimate from the work of Hoek et al. (2013) for long-term adult mortality attributable to $PM_{2.5}$. After HRAPIE, new single-pollutant and two-pollutant effect estimates from meta-analyses (Chen and Hoek, 2020; Pope et al., 2020) and from large European studies (Beelen et al., 2014; Stafoggia et al., 2022; Strak et al., 2021) have been published. Large European studies such as ESCAPE (European Study of Cohorts for Air Pollution Effects) (Beelen et al., 2014) and more recently ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) (Stafoggia et al., 2022; Strak et al., 2021) included cohorts exclusively located in Europe. The European Respiratory Society (ERS) and the International Society for Environmental Epidemiology (ISEE) jointly recommended in 2022 the use of ELAPSE effect estimates for Europe (Brunekreef et al., 2022; Hoffmann et al., 2022), because "ELAPSE is the largest study in Europe by far, designed specifically to address the effects of exposure to low levels of air pollution—below current EU air quality limit values—and represents the latest and most relevant data for Europe" (Hoffmann et al., 2022).

ELAPSE provided two different sets of effect estimates in two publications: a) a pooled analysis of eight prospective cohorts (none of them in Switzerland), i.e. pooling cohort data into one single European cohort (Strak et al., 2021) and b) a meta-analysis of seven European administrative cohorts, including the Swiss National Cohort (contributing to 15% of the study population) (Stafoggia et al., 2022). The prospective cohorts provided detailed data on individual lifestyle factors for confounding control, whereas the administrative cohorts mostly lacked adjustment for individual lifestyles, but provided large population samples with virtual no selection bias. Pros and cons of each ELAPSE effect estimate set have been broadly analyzed in a project research report (Brunekreef et al., 2021). Given the challenging choice between the two ELAPSE effect estimate sets, the ERS-ISEE effort recommended summary estimates (i.e. meta-analytic means) of both (Brunekreef et al., 2022; Hoffmann et al., 2022), referred to here as the ERS-ISEE effect estimates. However, ERS-ISEE only provided summary estimates of long-term mortality attributable to $PM_{2.5}$ and NO_2 as single-pollutant effect estimates, not as two-pollutant effect estimates. The single-pollutant summary estimates recommended in the ERS-ISEE joint statement were based on the effect estimates from the pooled prospective European cohort, which were directly adjusted for individual lifestyles, and the effect estimates from the seven administrative cohorts, which were only indirectly adjusted for lifestyle being smoking and body mass index (BMI) (Brunekreef et al., 2021, Table 22). Such effect estimates with indirect adjustment were not available for two-pollutant models in each single administrative cohort (only the result of the meta-analysis was available).

The goal of our study is to quantify the long-term adult mortality (premature deaths and years of life lost) attributable to air pollution in Switzerland using: 1) a single-pollutant effect estimate for $PM_{2.5}$ recommended in the joint statement of the ERS-ISSE, and 2) newly derived two-pollutant effect estimates for $PM_{2.5}$ and NO_2 based on ELAPSE cohort data, that can be used to add up the independent health impacts of pollutants. The results are to be compared with those when using alternative single-pollutant or two-pollutant effect estimates available in the literature.

2. Methods

2.1. General approach

2.1.1. Scope of research

The focus of our study in the frame of the project QHIAS (Quantification of Health Impact of Air pollution in Switzerland) is on natural cause mortality among adults attributable to long-term exposure to $PM_{2.5}$ and NO_2 in Switzerland in 2019. Since our study focused on mortality leaving morbidity out of the quantification, we refer to this hereinafter as air pollution mortality risk assessment (AP-MRA). We quantified adult mortality (often referring to ages 30 and older) and not infant mortality because the former is much higher (ARE, 2014).

$PM_{2.5}$, NO_2 and O_3 are the air pollutants most frequently considered in AP-MRAs for Switzerland (Castro et al., 2022). For our study, $PM_{2.5}$ was selected as indicator of both primary and secondary pollution and NO_2 as indicator of primary pollution from traffic. O_3 was excluded because only short-term exposure to O_3 shows a (likely) causality on natural-cause mortality (Vicedo-Cabrera et al., 2020), while long-term effects are less conclusive (Kutlar Joss et al., 2020). Only two-pollutant (i.e. not three-pollutant) effect estimates are available from ELAPSE.

We chose 2019 as year of analysis because this was the most recent year before the SARS-CoV2-pandemic, which had an impact on unusual high baseline mortality data in 2020 and 2021 in Switzerland (FSO, 2022b).

Finally, we aimed at the assessment of mortality in terms of both premature deaths and years of life lost.

2.1.2. Quantification of health impacts

When applying a single-pollutant approach, only the single-pollutant effect estimate for $PM_{2.5}$ was used as traditional main proxy for ambient air pollution. For the aggregation of premature deaths (and YLLs) applying a two-pollutant approach, we firstly calculated the health burden for $PM_{2.5}$ with an effect estimate from a two-pollutant model adjusted for NO_2 and vice versa (i.e. the health effects for NO_2 using an effect estimate from a two-pollutant model adjusted for a pollutant $PM_{2.5}$). Secondly, we summed both health impacts (Fig. 1).

We applied a life table method for the quantification of health impacts. Therefore, instead of a single value for the baseline health data, life tables, i.e. tables showing the probability of dying by age and sex, were used. Details on the life-table method and equations involved in the

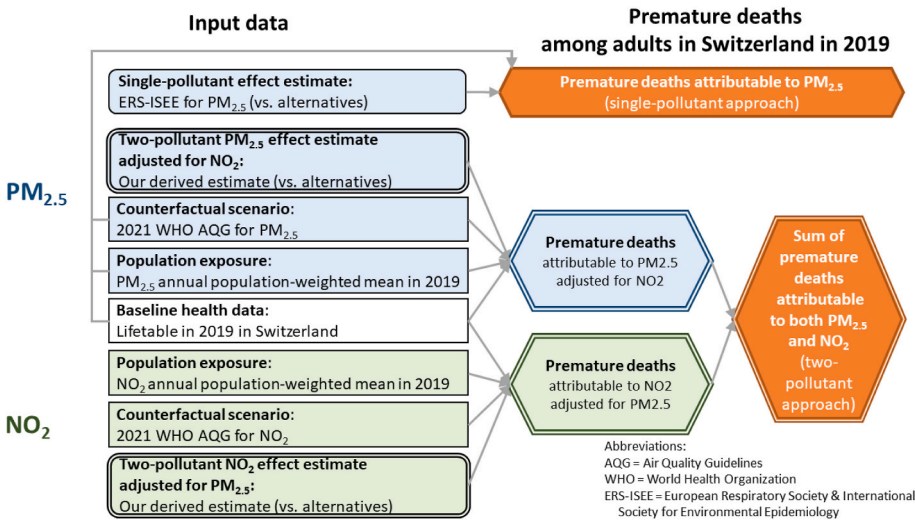

Fig. 1. Quantification of mortality attributable to $PM_{2.5}$ alone (single-pollutant approach) and both $PM_{2.5}$ and NO_2 (two-pollutant approach).

calculation of the number of deaths and years of life lost can be found in Appendix A.

2.2. Input data

2.2.1. Population exposure

We used population exposure data from the Swiss exposure model PolluMap (Künzle, 2021). This is a dispersion model with a resolution of 100 m × 100 m. The company Meteotest provided the population-weighted annual mean concentrations for $PM_{2.5}$ (8.3 μg/m^3) and NO_2 (16.32 μg/m^3) in Switzerland in 2019 (Meteotest, 2022). The exposure data were not stratified by age group.

2.2.2. Counterfactual scenario

As counterfactual scenario, we used the values of the 2021 Air Quality Guidelines suggested by the WHO (WHO, 2021) for $PM_{2.5}$ (5 μg/m^3) and for NO_2 (10 μg/m^3). These values reflect the lowest concentration with scientific evidence of health effects. Therefore, we assumed in our AP-MRA that no health effects occur below this concentration and subtracted the concentration of the counterfactual scenario from the population exposure.

2.2.3. Baseline health data

The Swiss Federal Statistical Office provided the baseline health data as natural mortality and the life tables (FSO, 2022a). We utilized different data sets for males and females by age. We obtained the annual number of natural deaths by subtracting the number of non-natural deaths from the all-cause deaths. To avoid the bias of outlier years, we considered the average mortality of the ten-year period from 2009 to 2019 and the average probability of dying from lifetables within the five-year period 2015–2019 for each sex and each age. The population data referred to the average at the end of 2018 and 2019. We considered adult people at the age of 30 or older, assuming that population younger than 30 is marginally affected by long-term mortality attributable to air pollution.

2.2.4. Effect estimates

2.2.4.1. Our selected estimates. For the single-pollutant approach, we used the ERS-ISEE estimate, i.e. 1.118 [1.060; 1.179] per 10 μg/m^3 $PM_{2.5}$, which is a summary estimate of the ELAPSE prospective and administrative cohorts. Regarding the two-pollutant approach, ERS-ISEE did not provide specific recommendation for effect estimates (Brunekreef et al., 2022; Hoffmann et al., 2022). We obtained the two-pollutant effect estimates by multiplying the ERS-ISEE single-pollutant effect estimates for $PM_{2.5}$ and NO_2 by pollutant-specific conversion factors. The resulting two-pollutant effects estimates were 1.023 [1.012; 1.035] per 10 μg/m^3 $PM_{2.5}$ adjusted for NO_2 and 1.040 [1.023; 1.058] per 10 μg/m^3 NO_2 adjusted for $PM_{2.5}$ (Table 2).

The conversion factors were calculated as the ratio between single-pollutant and two-pollutant effect estimates from a same model, following the approach of the COMEAP in their AP-MRA for $PM_{2.5}$ and NO_2 (COMEAP, 2018). The single-pollutant and two-pollutant effect estimates used to obtain the conversion factor were the summary estimates (i.e. meta-analytic means of the effect estimates) from the prospective and administrative ELAPSE cohorts (Fig. 2). We used the analyses without indirect adjustment for lifestyles in the administrative cohorts since for these analyses both the single-pollutant and two-pollutant effect estimates were available at cohort level (Brunekreef et al., 2021; Additional material 3, table A 23). The models with indirect adjustment, which were used for the ERS-ISEE effect estimates, were only available for single-pollutant.

To pool the summary estimates, we carried out a random effects meta-analysis with generic inverse variance. We treated the seven administrative cohorts (Stafoggia et al., 2022) individually, while we treated the eight prospective cohorts included in the pooled European cohort (Strak et al., 2021) as one single cohort, like in the original publication and the joint statement of the ERS-ISEE (Brunekreef et al., 2022; Hoffmann et al., 2022).

2.2.4.2. Alternative effect estimates for the comparison. Beyond the effect estimates that we selected for our study, other single-pollutant and two-pollutant effect estimates from the literature might be alternatively used for an AP-MRA for Switzerland. We compared the resulting mortality of the AP-MRA using our selected effect estimates with the alternatives. Table 1 shows the effect estimates that we included in the comparison. We mainly considered effect estimates for Europe. Exceptionally, we also considered the global estimate of Hoek et al. (2013) because it was recommended by the WHO project HRAPIE and the ELAPSE country-specific effect estimates for Switzerland from the Swiss administrative cohort (Stafoggia et al., 2022).

Some effect estimates for $PM_{2.5}$ and NO_2 were originally expressed as per 5 μg/m^3 increment, while others per 10 μg/m^3. To obtain the effect estimates corresponding to any other increment in concentration, we assumed a log-linear shape of the concentration-response function, as recent AP-MRAs (e.g. Khomenko et al., 2021), applying Equation 1.

Equation 1 Effect estimate after a change in the concentration increment.

$$EE_1 = e^{\ln(EE_0)*\frac{C_1}{C_0}} \quad \left| \begin{array}{c} EE1 = \textit{Effect estimate for the target concentration increment } C1. \\ EE0 = \textit{Effect estimate for the original concentration increment } C0 \textit{ as in literature}. \\ C0 = \textit{Original concentration increment of the effect estimate } (e.g.\ 10 \textit{ or } 5\ \mu g/m3). \\ C1 = \textit{Target concentration increment}. \end{array} \right.$$

2.3. Materials

For the data analysis and visualization, we programmed in R language (version 4.0.3) (R Core Team, 2020) using R Studio (version 1.3.1093) (RStudio Team, 2020). Additionally, the following R packages were used: zoo (Zeileis and Grothendieck, 2005), meta (Balduzzi et al., 2019) as well as tidyverse packages (Wickham et al., 2019) such as readxl (Wickham and Bryan, 2022), dplyr (Wickham et al., 2022), tidyr (Wickham and Girlich, 2022), purrr (Henry and Wickham, 2020), tibble (Müller and Wickham, 2022), stringr (Wickham, 2022) and ggplot2 (Wickham, 2016). For the figures, we used a colorblind-friendly palette (Okabe and Ito, 2008).

3. Results

3.1. Using our selected effect estimates

3.1.1. Single-pollutant approach

Using the single-pollutant effect estimate for $PM_{2.5}$ recommended in the joint statement of the ERS-ISEE, we found that 2240 premature deaths (21,593 years of life lost) among adults in Switzerland in 2019 were attributable to $PM_{2.5}$ (Table 3).

3.1.2. Two-pollutant approach

Applying the two-pollutant effect estimates resulted in a total of 1977 premature deaths (19,071 years of life lost) among adults attributable to long-term ambient exposure to $PM_{2.5}$ and NO_2 in Switzerland in 2019 (Table 3). This is an 11.7% lower number attributable mortality than obtained from the single-pollutant approach (1977 vs. 2240 deaths). Out of the total attributable mortality with the two-pollutant approach, 23% (461 deaths, 4.447 years of life lost) was attributable to $PM_{2.5}$ and 77% (1516 deaths, 14,624 years of life lost) to NO_2 (Table 3).

3.2. Using alternative effect estimates

When using alternative single-pollutant and two-pollutant effect estimates, the quantified adult mortality for Switzerland in 2019 ranged from 1042 to 5059 premature deaths (Fig. 3). Thus, the 2040 deaths from the ERS-ISEE single-pollutant effect estimate for $PM_{2.5}$ and the 1977 deaths from our two-pollutant effect estimate for $PM_{2.5}$ and NO_2 (called "QHIAS-AdjustingERS-ISEE" in Fig. 3) are within the range of the results using the alternative effect estimates. The two lowest attributable number of deaths were obtained when applying the single-pollutant effect estimate for $PM_{2.5}$ from the Swiss administrative cohort of ELAPSE project (Stafoggia et al., 2022) (1042 deaths) and from the WHO project HRAPIE (Hoek et al., 2013) (1218 deaths). In contrast, the highest attributable number of premature deaths was reached when using the effect estimates from pooled European prospective cohort of ELAPSE (Strak et al., 2021); 5059 deaths with a two-pollutant approach and 4803 with a single-pollutant approach (Fig. 1).

It should be noted that not only our selected effect estimates resulted in higher number of premature deaths attributable to $PM_{2.5}$ alone applying a single-pollutant approach than the number attributable to both $PM_{2.5}$ and NO_2 applying a two-pollutant approach. This pattern was also observed in some alternative effects estimates where the pair single-pollutant and two-pollutant estimates were available from the same model. The number of premature deaths applying a single-pollutant approach was 21.2% higher than the two-pollutant approach (2076 vs. 1713) when using the effect estimates based on the seven European administrative cohorts from ELAPSE (Stafoggia et al., 2022), and 3.7% (2706 vs. 2611) using the older project ESCAPE (Beelen et al., 2014). On the contrary, in the case of the European prospective pooled cohort (Strak et al., 2021) and the Swiss administrative cohort (Stafoggia et al., 2022), both from ELAPSE, the two-pollutant approach resulted in a higher number of premature deaths than the single-pollutant approach. The confidence interval of the premature deaths from two-pollutant approaches was higher than the single-pollutant in all pairs.

The individual contribution of each pollutant in two-pollutant

Table 1
Conversion of single-pollutant effect estimates into two-pollutant effect estimates for $PM_{2.5}$ or NO_2 using ELAPSE data. Conversion factors obtained from Figure A 1 to Figure A 4 (Appendix B).

Single-pollutant effect estimates from ERS-ISEE [a]		Calculation of conversion factors				Derived two-pollutant effect estimates [c]
Pollutant	Effect estimate per 10 μg/m^3 [confidence interval]	Mean single-pollutant effect estimate per 10 μg/m^3 [b]	Mean two-pollutant effect estimate per 10 μg/m^3 [b]	Adjusted for	Conversion factor	Effect estimate per 10 μg/m^3 [95% confidence interval]
	EE_{1P}	EE_{CF1}	EE_{CF2}		CF	EE_{2P}
					$\frac{1-EE_{CF2}}{1-EE_{CF1}}$	$(1-EE_{1P}*CF)+1$
$PM_{2.5}$	1.118 [1.06; 1.179]	1.128	1.025	NO_2	0.194	1.023 [1.012; 1.035]
NO_2	1.045 [1.026; 1.065]	1.049	1.043	$PM_{2.5}$	0.889	1.040 [1.023; 1.058]

Abbreviations: ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe. ERS-ISEE: European Respiratory Society and International Society for Environmental Epidemiology.

[a] Summary estimate of ELAPSE cohorts using models with indirect adjustment for lifestyles (Brunekreef et al., 2022; Hoffmann et al., 2022).

[b] We obtained these values by means of a random effects meta-analysis among the ELAPSE models for the pooled European cohort with adjustment for lifestyles as well as for the seven administrative cohorts without adjustment for lifestyles (Brunekreef et al., 2021, Table 22) (see Appendix B). The estimates for $PM_{2.5}$ were originally expressed as per 5 μg/m^3 for $PM_{2.5}$ and after the meta-analysis, we standardized the increment to 10 μg/m^3 using Equation 1.

[c] Two-pollutant ERS-ISEE obtained by adjusting the single-pollutant effect estimates for another pollutant following the approach of COMEAP (COMEAP, 2018).

Table 2
Effect estimates considered in the comparison including the ERS-ISEE and alternative estimates.

Source	Description	Effect estimate standardized per 10 μg/m^3 [95% confidence interval]		
		Single-pollutant	Two-pollutant	
		$PM_{2.5}$	$PM_{2.5}$ adjusted for NO_2	NO_2 adjusted for $PM_{2.5}$
Selected effect estimates				
ERS-ISEE (Brunekreef et al., 2022; Hoffmann et al., 2022)	Summary (pooled) estimate of European ELAPSE prospective and administrative cohorts (the former adjusted for lifestyle, the latter indirectly adjusted for lifestyle).	1.118 [1.060; 1.179]		
Our two-pollutant effect estimate	After converting the single-pollutant ERS-ISEE estimates into two-pollutant estimates in the framework of the project QHIAS (see Section 2.2.4.1).		1.023 [1.012; 1.035]	1.040 [1.023; 1.058]
Alternative effect estimates				
Beelen et al. (2014)	Pooled effect analysis of the project ESCAPE across 22 European cohorts (including Switzerland).	1.145 [1.032; 1.270] [a]	1.124 [0.955; 1.322] [a]	1.007 [0.967; 1.049]
Chen and Hoek (2020)	Subgroup results of meta-analysis of five European studies (including ESCAPE).	1.070 [1.030; 1.110]		
Hoek et al. (2013)	Global estimate from meta-analysis of 11 studies (two in Europe, nine in North America). Recommended by the WHO project HRAPIE and used in STE-2010.	1.062 [1.040; 1.083]		
Pope et al. (2020)	Subgroup results of meta-analysis of 10 European studies (including ESCAPE).	1.120 [1.060; 1.190]		
Stafoggia et al. (2022)	Seven European administrative cohorts (including Switzerland) without adjustment for lifestyle (except in England) from the project ELAPSE.	1.109 [1.042; 1.177] [a]	1.006 [0.964; 1.051] [a]	1.042 [1.020; 1.065]
	Swiss administrative cohort without adjustment for lifestyle from the project ELAPSE.	1.053 [1.030; 1.077] [a]	0.984 [0.956; 1.010] [a]	1.053 [1.043; 1.063]
Strak et al. (2021)	Eight European pooled prospective cohort adjusted for lifestyle from the project ELAPSE.	1.277 [1.223; 1.334] [a]	1.173 [1.111; 1.239] [a]	1.050 [1.031; 1.070]

Abbreviations: ELAPSE = Effects of Low-Level Air Pollution: A Study in Europe. ERS-ISEE: European Respiratory Society and International Society for Environmental Epidemiology. ESCAPE = European Study of Cohorts for Air Pollution Effects. HRAPIE= Health risks of air pollution in Europe. QHIAS = Quantification of Health Impact of Air Pollution in Switzerland. WHO = World Health Organization.

[a] The effect estimate was originally expressed in the source as per 5 μg/m^3. See the original values in Table A 1 (Appendix B).

approaches varied across the alternative effect estimates considered in our study (Table 4). As for our selected two-pollutant effect estimates, the number of premature deaths attributable to $PM_{2.5}$ was lower than to NO_2 for the estimates from the European ELAPSE administrative cohorts of Stafoggia et al. (2022) (123 vs. 1,590, i.e. 7% of the total). In contrast, the deaths attributable to $PM_{2.5}$ than to NO_2 in the case of the effect estimates from the work of Beelen et al. (2014) (2338 vs. 273) and the ELAPSE prospective cohorts of Strak et al. (2021) (3177 vs. 1882). The two-pollutant effect estimate for $PM_{2.5}$ adjusted for NO_2 from the Swiss administrative cohort of the ELAPSE project was lower than 1, which resulted in a negative number of deaths that was compensated by the effect from NO_2. This negative number is not to be interpreted as a beneficial health effect, but as a consequence of the inexactness of the effect estimate.

The years of life lost attributable to $PM_{2.5}$ alone and to both $PM_{2.5}$ and NO_2 (single-pollutant and two-pollutant approach respectively) by alternative effect estimate are available in Figure A 5 and Table A 2 (Appendix C).

4. Discussion

4.1. Main findings

Using the single-pollutant ERS-ISSE effect estimate for $PM_{2.5}$, which is based on European ELAPSE cohorts, we found 2240 premature deaths (21,593 years of life lost) attributable to $PM_{2.5}$ in adults in Switzerland in 2019. Applying a two-pollutant approach, yielded an overall lower attributable mortality (1977 deaths, 19,071 years of life lost). Of the total mortality, 23% was attributable to $PM_{2.5}$ and 77% to NO_2, respectively. We derived the two-pollutant effect estimates by applying pollutant-specific conversion factors to the single-pollutant effect estimates suggested in the joint statement of the ERS-ISEE, all of them from ELAPSE cohort data.

The number of premature deaths obtained using our selected single-pollutant and two-pollutant effect estimates were within the range of these alternative results, which ranged between 1042 and 5059. Surprisingly, using a single-pollutant effect estimate resulted in a higher number of premature deaths than summing the mortality attributable to $PM_{2.5}$ and NO_2 using two-pollutant effect estimates in our selected effect estimates and in some alternative effect estimates from the ELAPSE administrative cohorts. Furthermore, the proportion of deaths attributable to $PM_{2.5}$ was smaller than to NO_2 in both our selected two-pollutant estimates and some alternatives from ELAPSE administrative cohorts.

4.2. Interpretation and implications

A comparison of our results with other similar publications is limited because the two-pollutant approach, i.e. the aggregation of the health effects of $PM_{2.5}$ and NO_2 with the use of two-pollutant effect estimates mutually adjusted for both pollutants, has been rarely applied in APMRAs. An exception is the application of the two-pollutant approach undertaken by COMEAP (COMEAP, 2018; Gowers et al., 2020). COMEAP also derived the two-pollutant effect estimates from single-pollutant effect estimates, as we did, but converting robustly established single-pollutant effect estimates for $PM_{2.5}$ and NO_2 from Hoek et al. (2013) and from an ad-hoc meta-analysis (COMEAP, 2018), respectively. To calculate the conversion factor, the single-pollutant and two-pollutant effect estimates from the project ESCAPE (Beelen et al., 2014), among other three non-European alternatives, were used. Our and COMEAP's effect estimates for $PM_{2.5}$ were quite similar, while the effect estimates for NO_2 resulted in a much higher estimate in our case. Thus, the mean excess risk estimate of our derived effect estimates was 58.2% lower than those from COMEAP for $PM_{2.5}$ adjusted for NO_2 (0.023 vs. 0.053) and 3.6 times higher for NO_2 adjusted for $PM_{2.5}$ (0.040 vs. 0.011). This can be explained by the percentage of reduction of conversion factors. Our conversion factors reduced the $PM_{2.5}$ and NO_2

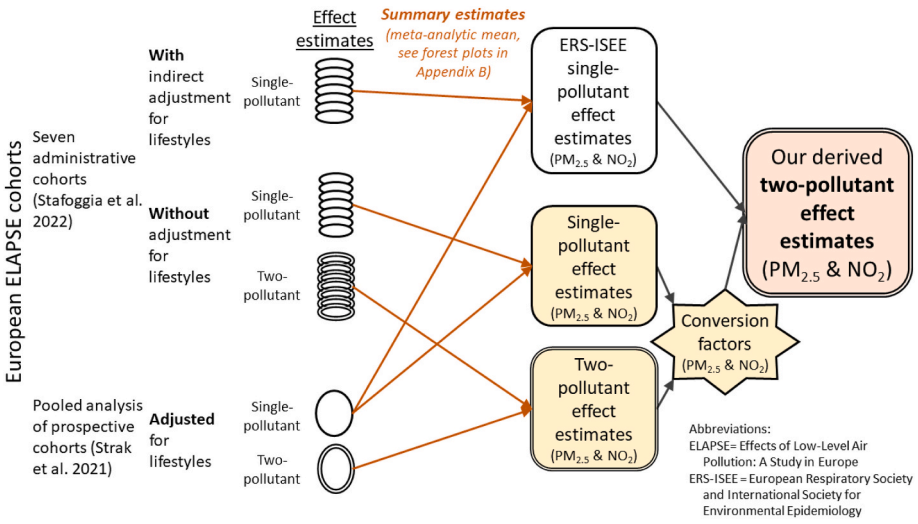

Fig. 2. Conversion of single-pollutant into two-pollutant effect estimates.

Table 3
Number of premature deaths among adults in 2019 in Switzerland attributable to both $PM_{2.5}$ and NO_2 using our derived two-pollutant effect estimates converted from the ERS-ISEE single-pollutant effect estimates.

Approach	Pollutant	Effect estimate per 10 μg/m^3 [95% confidence interval]	Premature deaths		Years of life lost	
			By pollutant	Total among pollutants	By pollutant	Total among pollutants
Single-pollutant	$PM_{2.5}$	1.118 [1.060; 1.179]	2240	2240	21,593	21,593
Two-pollutant	$PM_{2.5}$	1.055 [1.028; 1.084]	461	1977	4447	19,071
	NO_2	1.040 [1.023; 1.058]	1516		14,624	

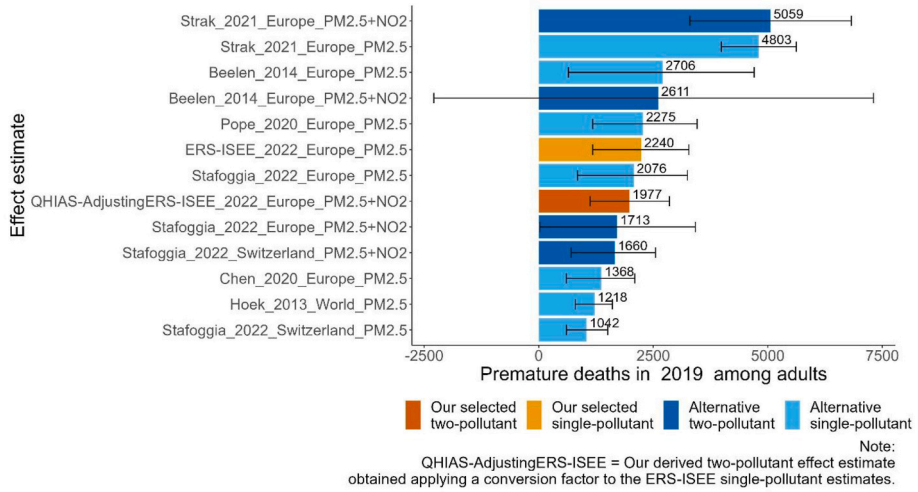

Fig. 3. Premature deaths among adults in 2019 in Switzerland attributable to $PM_{2.5}$ alone (single-pollutant approach) or to the sum of $PM_{2.5}$ and NO_2 mutually adjusting health effects (two-pollutant approach) using different effect estimates. The confidence intervals show the mortality when using the lower and upper bound of the effect estimates.

single-pollutant effect estimates by 80.6% and 11.1% respectively, while the COMEAP's conversion factors based on effect estimate of ESCAPE (Beelen et al., 2014) reduced them by 14% and 53%. Advances in modelling and exposure assessment together with the specific focus of ELAPSE on low-level air pollution as well as the lack of full adjustment for lifestyle of administrative cohorts may play a role in such differences in effect estimates. This shows that mutual adjustment can introduce substantial statistical variations, given the relatively low excess risks with relatively wide confidence intervals.

In light of our resulting premature deaths, some pros and cons associated with the use of our derived two-pollutant effect estimates in AP-MRAs are pointed out below. Our derived two-pollutant effect estimates resulted in a number of premature deaths that can be considered as moderate in comparison with other alternative effect estimates relevant for Europe, regarding both single-pollutant and two-pollutant approaches. The fact that our derived effect estimates do not lead to relatively high attributable mortality is not itself an argument to use them, but it is indeed a sign that the effect estimates do not lead to outlier results that challenge communication, especially for policy making. Furthermore, our effect estimates enabled the inclusion of more

Table 4
Number of premature deaths among adults in Switzerland in 2019 attributable to both $PM_{2.5}$ and NO_2 using alternative two-pollutant effect estimates.

Study	Pollutant	Effect estimate per 10 μg/m^3 [95% confidence interval]	Resulting premature deaths	
			By pollutant	Total of summing deaths from $PM_{2.5}$ and NO_2
Beelen et al. (2014)	$PM_{2.5}$	1.124 [0.955; 1.322]	2338	2611
	NO_2	1.007 [0.967; 1.049]	273	
Stafoggia et al. (2022) – seven European administrative cohorts	$PM_{2.5}$	1.006 [0.964; 1.051]	123	1713
	NO_2	1.042 [1.020; 1.065]	1590	
Stafoggia et al. (2022) – only Swiss administrative cohort	$PM_{2.5}$	0.984 [0.956; 1.010]	−330	1660
	NO_2	1.053 [1.043; 1.063]	1990	
Strak et al. (2021)	$PM_{2.5}$	1.173 [1.111; 1.239]	3177	5059
	NO_2	1.050 [1.031; 1.070]	1882	

than one pollutant in the AP-MRA adding health effects among pollutants, since they are adjusted for other pollutants. This helps to understand how much each air pollutant contributes to the total resulting mortality. To the extent that NO_2 remains a marker more directly related to traffic emissions, this is of special relevance for studies on transport externalities such as the specific Swiss assessments (ARE, 2014).

On the other hand, our two-pollutant approach led to results with challenges in interpretation. The higher number of premature deaths attributable to $PM_{2.5}$ alone (single-pollutant approach) compared to the sum of deaths from both $PM_{2.5}$ and NO_2 (two-pollutant approach) may seem counterintuitive. Furthermore, the smaller proportion of premature deaths from $PM_{2.5}$ than from NO_2 (23.3% vs. 76.7%) in the two-pollutant approach may seem inconsistent with the idea that $PM_{2.5}$ is the main criteria air pollutant, and therefore often used as single indicator. Similar patterns were found in some of the alternative effect estimates from the ELAPSE administrative cohorts.

Both seemingly paradoxical results, i.e. the higher number of deaths using the single-pollutant approach than the two-pollutant approach and the higher proportion of deaths attributable to NO_2 than to $PM_{2.5}$, have a common explanation: the two-pollutant $PM_{2.5}$ effect estimate after adjusting for NO_2 of the administrative cohorts of ELAPSE (Stafoggia et al., 2022) is very low (close to 1). The reason for this low value has been documented in the research report that extensively compared the ELAPSE effect estimate data sets, but the authors did not find "a clear explanation" for this attenuation (Brunekreef et al., 2021). They concluded that "because the correlation between $PM_{2.5}$ and NO_2 was moderate and the width of the CI [confidence interval] was only modestly increased in two-pollutant models, the reduction of the $PM_{2.5}$ HR [hazard ratio] cannot be interpreted as an artefact related to multi-collinearity". A high correlation between air pollutants makes difficult to disentangle the effect of each pollutant separately. COMEAP recommended to use the two-pollutant effect estimates only if there is low correlation (lower than 0.7) between $PM_{2.5}$ and NO_2 in the multi-pollutant studies. This is more or less the case in the ELAPSE pooled prospective cohort (0.2–0.77) (Strak et al., 2021) and in the administrative cohorts (0.51–0.86) (Stafoggia et al., 2022), but the upper bound exceed the boundary recommended by the COMEAP.

The lower effect estimate for $PM_{2.5}$ than for NO_2 after mutually adjusting for each other has been also found in a publication that produced two-pollutant models for several air pollutants and noise in Switzerland extending the analysis of ELAPSE data (Vienneau et al., 2023). The authors of the ELAPSE research report "did not interpret the reduction of the $PM_{2.5}$ HR [hazard ratio] as implying that in the setting, particles had no effect, as adjustment for NO_2 also adjusted for particles from the sources shared with NO_2, including motorized traffic and other sources of fossil fuel combustion" (Brunekreef et al., 2021). This demonstrates that prudent interpretation of the effect estimates in terms of causal effects is advised, which implies that the obtained results do not fit with the overall motivation for applying a two-pollutant approach, i.e. attributing health effects to specific pollution sources.

In the case of the Swiss ELAPSE administrative cohort, the two-pollutant effect estimate for $PM_{2.5}$ was lower than 1, which led to non-significant negative results. The smaller study population of this cohort compared to the estimate from the seven cohorts results in higher random variability and indicates that effect estimates should be derived from large database such as pooled analyses or meta-analyses.

It should also be acknowledged that the use of our conversion factor to pass from single-pollutant to two-pollutant effect estimates was quite simplistic and assumed no overlapping or added effects. If this assumption is not hold, this might also be an explanation for the seemingly paradoxical results of our two-pollutant effect estimates and not only statistical variation. The application of different counterfactuals for multiple pollutants adds an additional layer of complexity to the calculation contributing to change the proportion of each pollutant in the total assessment.

With the above explanation in mind, it is important to not falsely communicate such AP-MRA results (especially for policy making) as evidence for $PM_{2.5}$ to be irrelevant for health. Instead, it shows the methodological challenges in sorting out the specific contributions of interrelated pollutants to the overall burden of death. The difficulty of two-pollutant effect estimates is that the causal effects are implicitly disentangled based on the correlation of the pollutants. However, correlation may be determined by several factors such as the accuracy of exposure modelling or correlation with other unmeasured air pollutants and risk factors, and thus not necessary directly represent causation. In Switzerland, $PM_{2.5}$ is mainly a surrogate for background air pollution including long-range transported and secondary formed pollutants, whereas NO_2 is a surrogate for primary air pollutants from combustion such as traffic or concrete industry.

It is worth mentioning that the results of the AP-MRA are very sensitive to small changes in input data and methods. Therefore, the decision on single-pollutant vs. two-pollutant approach and the choice of the effect estimate has to be carefully and transparently done to show the reasons behind a likely under- or overestimation of the attributable mortality.

Beyond the choice of the effect estimate, the counterfactual scenario can also affect the result of AP-MRA. The authors of the 2021 WHO Air Quality Guidelines pointed out that "the available evidence cannot currently identify levels of exposure that are risk free […]" (WHO, 2021), but they defined air quality guidelines level as the concentration at which "it is assumed that adverse health effects do not occur or are minimal below this concentration" (WHO, 2021). Some AP-MRAs (and AP-HRAs) with specific results for Switzerland did not consider any cut-off in the quantification (e.g. ETC/ACM 2016), while more commonly (e.g. ARE, 2014; Khomenko et al., 2021; Murray et al., 2020; WHO, 2016a) some kind of cut-off was applied (Castro et al., 2022). Our counterfactual scenario served as a cut-off. This approach can be considered as conservative, because if we had not apply the cut-off, the results of our AP-MRA would have been higher.

4.3. Limitations

We converted the ERS-ISEE single-pollutant effect estimates into two-pollutant effect estimates. The resulting two-pollutant effect estimates did not fully preserve the adjustment for lifestyles of the ERS-ISEE

because we had to use a conversion factor without such adjustment in the administrative ELAPSE cohorts. The models of the administrative cohorts were not adjusted for individual lifestyles, in contrast to those from ERS-ISEE, which were indirectly adjusted for lifestyle (including smoking and BMI). We used these non-adjusted models because no better alternative was available. Specifically, no two-pollutant effect estimate with indirect adjustment for each administrative cohorts were published in the ELAPSE study (Stafoggia et al., 2022) or in the research report (Brunekreef et al., 2021).

Alternatively to NO_2, black carbon (or elemental carbon) could have been used in combination with $PM_{2.5}$ in our two-pollutant approach. However, two-pollutant AP-MRAs for this combination are scarce and exposure assessments for black/elemental carbon may also not be easily available (compared to NO_2).

According to the Integrated Science Assessment for O_3 of the United States Environmental Protection Agency, the evidence of causality of exposure to O_3 on natural mortality is suggestive but not sufficient (US EPA, 2020). The WHO project HRAPIE suggested to use O_3 effects estimates for natural mortality only for short-term exposure (WHO 2013). There is strong agreement on the causal evidence of short-term health effects of O_3 with suitable effect estimates (Vicedo-Cabrera et al., 2020). Since short-term exposure to O_3 is not correlated to long-term exposure to $PM_{2.5}$ or NO_2, the former could have been included as an independent additional air pollutant in the AP-MRA, without the need of the more complicated double-counting corrections as done for $PM_{2.5}$ and NO_2. However, no daily spatial modelling data for O_3 are currently available to derive the population-weighted exposure for Switzerland. If the evidence of causality of long-term exposure to O_3 on natural mortality increases, long-term O_3 effect estimates (also provided by ELAPSE) could be considered in future assessments.

In contrast to the Global Burden of Disease (2019) study (Murray et al., 2020), which estimated mortality summing cause-specific mortality, we estimated natural mortality. Moreover, this study used age specific effect estimates, unlike our considered all-ages effect estimates. For those reasons, we could not include the effect estimates from the Global Burden of Disease study in our comparison of effect estimate.

4.4. Future research

Given that we used the WHO Air Quality Guidelines 2021 as counterfactual scenario, the results in our study also reflect the mortality that could have been avoided in Switzerland in 2019, if the air pollution exposure had not exceed the level of WHO Air Quality Guidelines. The monetarization of health benefits of reducing air pollution to WHO Air Quality Guidelines levels is of use for policy-making (Egerstrom et al., 2023) and could be part of future Swiss research.

The conversion of single-pollutant effect estimates into two-pollutant effect estimates was needed, because the ERS-ISEE effect estimates were available only as single-pollutant. The two-pollutant effect estimates with indirect adjustment for lifestyles for each ELAPSE administrative cohort were not available. If future publications provide new robust two-pollutant effect estimates for Europe, the above mentioned conversion would not be needed anymore.

Future epidemiological studies might provide effect estimates from multi-pollutant models mutually adjusting for more than two pollutants. Such models might ideally take into account the "cocktail" effect, i.e. the combined effect as a result of the interaction of multiple air pollutants. However, as the example from ELAPSE showed, high correlations between pollutants such as NO_2 and black/elemental carbon preclude having both in the same model (Strak et al., 2021). Alternatively, a different approach including the residuals of the linear regression using $PM_{2.5}$ as independent variable and further pollutants as dependent variables could be applied (Yang et al., 2021).

Source-specific AP-MRAs (e.g. assessments for transport externalities) may aim to quantify health impacts of each of the sources of pollution instead of relying on few pollutants. Carrying out source-specific AP-MRAs would enable concrete information on the contribution of each pollution source on the total health burden. This information is of particular interest to design public policies for better air quality. However, the application of such source-specific approaches is not possible yet. Solid source-specific epidemiological and Swiss exposure data are currently scarce.

5. Conclusion

In contrast to traditional single-pollutant effect estimates, two-pollutant effect estimates enable the quantification of health effects mutually attributable to various pollutants. In the last years, new mutually adjusted two-pollutant effect estimates that are relevant for Europe have been published. After deriving our two-pollutant effect estimates from the European cohorts of the project ELAPSE, we concluded that it is feasible to use them in AP-MRAs applying a two-pollutant approach for $PM_{2.5}$ and NO_2, i.e. summing the health effects of both pollutants adjusted for each other. However, we found that the two-pollutant approach lead to challenges in interpretation of the results, namely lower number of premature deaths for the two-pollutant than for single-pollutant approach and for $PM_{2.5}$ than for NO_2. Therefore, we suggest to apply a two-pollutant approach for $PM_{2.5}$ and NO_2 only if the AP-MRA has a strong focus on pollutant-specific or source-specific attributable mortality. Otherwise, a single-pollutant approach for $PM_{2.5}$ provides more robust and internationally comparable results.

Credit author statement

Alberto Castro: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Project administration. Nino Künzli: Conceptualization, Supervision, Funding acquisition. Kees de Hoogh: Methodology. Ron Kappeler: Writing - Review & Editing. Meltem Kutlar Joss: Writing - Review & Editing. Danielle Vienneau: Methodology, Writing - Review & Editing. Martin Röösli: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.116029.

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