Maternal age at delivery, lung function and asthma in offspring: a population-based survey

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ABSTRACT There is limited information about potential impact of maternal age on the respiratory health of offspring. We investigated the association of maternal age at delivery with adult offspring's lung function, respiratory symptoms and asthma, and potential differences according to offspring sex.

10 692 adults from 13 countries participating in the European Community Respiratory Health Survey (ECRHS) II responded to standardised interviews and provided lung function measurements and serum for IgE measurements at age 25–55 years. In logistic and linear multilevel mixed models we adjusted for participants' characteristics (age, education, centre, number of older siblings) and maternal characteristics (smoking in pregnancy, education) while investigating for differential effects by sex. Maternal age was validated in a subsample using data from the Norwegian birth registry.

Increasing maternal age was associated with increasing forced expiratory volume in 1 s (2.33 mL per year, 95% CI 0.34–4.32 mL per year), more consistent in females (p_{trend} 0.025) than in males (p_{trend} 0.14). Asthma (OR 0.85, 95% CI 0.79–0.92) and respiratory symptoms (OR 0.87, 95% CI 0.82–0.92) decreased with increasing maternal age (per 5 years) in females, but not in males ($p_{interaction}$ 0.05 and 0.001, respectively). The results were consistent across centres and not explained by confounding factors.

Maternal ageing was related to higher adult lung function and less asthma/symptoms in females. Biological characteristics in offspring related to maternal ageing are plausible and need further investigation.

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Introduction

Rapid demographic changes have occurred worldwide in past decades [1], including a substantial increase in maternal age at delivery. Females now tend to get pregnant later in life, particularly in the developed world [2]. Benefits and risks in terms of pregnancy complications are well known [3, 4]; however, there is very limited information about how maternal ageing influences offspring health in the long term. With regard to respiratory health, there are studies showing more asthma in persons born to younger mothers [5, 6], as well as studies showing contradictory results [7, 8]. A recent analysis found that lung function decline, a measure of lung ageing, was accelerated in persons born to mothers aged >31 years, consistent across European regions [9]. There are no studies addressing maternal age and lung function level, an important parameter of respiratory health and a strong predictor of general health, life expectancy and life quality. It is important to shed light on long-term respiratory health effects of maternal age at delivery, both to enhance understanding of the importance of reproductive factors for respiratory health and to assess potential consequences of demographic change for respiratory health.

Reproduction requires a fine-tuned balance between hormonal, metabolic, immunological and genetic factors; these are all likely to be involved in the ageing processes, and within the first three to four decades of reproductive age span in females. It is biologically plausible that maternal ageing should influence offspring health, and the extreme effects are reflected in decreased fertility with increasing maternal age. The short-term consequences of maternal age on the health of offspring are relatively well characterised, particularly with regard to pregnancy and delivery complications in very young and very old mothers [10–13]. Maternal age may affect pregnancy outcomes in a sex-specific manner [8]. In addition to the biological effects of maternal ageing, there are substantial socioeconomic differences between younger and older mothers. Older mothers are generally more affluent, have a higher level of education and more life experience [14].

We hypothesise that maternal age at delivery have long-term consequences for offspring respiratory health and that effects may differ between male and female offspring. The aims of the present study were firstly to assess the relationship between maternal age at delivery and adult lung function level, respiratory symptoms and asthma in the offspring; and secondly to investigate whether potential associations differed by sex of the offspring. The analyses were based on the European Community Respiratory Health Study (ECRHS), which provided information on maternal age at delivery, number of siblings and socioeconomic factors and detailed characterisation of offspring's respiratory health outcomes in adulthood, in a multinational and population-based setting.

Methods

The ECRHS [15] was established in 1992–1994 and recruited randomly selected individuals aged 20–44 years from general populations. Participants from 29 centres in 14 countries contributed to a follow-up, ECRHS II [16], in 1998–2002 (response rate 62%). At both surveys, an extensive interviewer-led questionnaire assessed information such as maternal age at delivery, maternal smoking in pregnancy, maternal asthma, living environment in early childhood, number of older and younger siblings and asthma and respiratory symptoms. Both surveys further included measurements of height and weight, lung function (forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)) and specific IgEs. The study is described at www.ecrhs.org. Complete data were available for 10 692 participants. Additional data were available on maternal educational level for 6303 ECRHS III participants, birth weight from hospital protocols for 2195 participants from Northern European centres and maternal age at delivery from Norwegian Medical Birth Registry for 329 participants born in 1967–1971 from Bergen. Ethical approval was obtained for each study centre from the appropriate ethics committees, and each participant provided informed written consent.

Additional detail on the methods is provided in the online supplementary material. A directed acyclic graph (DAG) [17] for the relationship between maternal age and offspring respiratory health was constructed. In order to identify minimally sufficient adjustment (MSA) sets, the model was analysed using the DAGitty software (version 2014-10-30) [18]. The identified MSA set included centre, maternal educational level and number of older siblings.

For lung function outcomes (FEV_1 in mL, FVC in mL, FEV_1/FVC ratio and decline in FEV_1 in mL·year^{-1} of follow-up), multilevel mixed linear models with centre as a random intercept were used to assess the associations with maternal age, with adjustments for age at ECRHS II, sex, height (m), maternal smoking during pregnancy, being a single child and number of older siblings. Maternal age was used either as a continuous variable (overall associations, per 5-year increase) or as a categorical (predicted levels of lung function stratified by sex). Multilevel mixed-effects logistic regressions were used to assess the association between maternal age at delivery (per 5-year increase) and asthma, respiratory symptoms and hay fever. Adjustments were made for centre as a random effect, maternal smoking in pregnancy and number of

older siblings. Differences between subgroups were analysed by means of stratified logistic regression models for respiratory symptoms, and by stratified linear regression models for lung function. Interaction terms of maternal age with sex, or being a single child, were included in the analyses. Potential heterogeneity between centres was studied and the centre effects were meta-analysed. Analyses were performed using STATA13 (StataCorp, College Station, TX, USA).

Sensitivity analyses

Sensitivity analyses with additional adjustment for maternal educational level were performed all outcomes in the subpopulation with available data, since maternal educational was identified as a potential confounder linked to maternal age and respiratory outcomes. Analyses stratified by number of older siblings were performed for all outcomes, since number of older siblings is so closely linked to maternal age. Additional sensitivity analyses were performed with adjustment for potential confounders often analysed by convention, including body mass index (BMI) ($kg \cdot m^{-2}$), smoking history and age/age difference between surveys for all outcomes, and including daycare attendance, childhood urban/rural living, maternal asthma and birthweight for asthma and symptoms. Lung function was analysed with exclusion of Melbourne data due to heterogeneity in ECRHS II measurements in this centre. Analyses restricted to those reporting maternal age at delivery at age 20–40 years were performed for asthma and symptoms to assess whether associations were driven by the youngest and oldest mothers.

Results

In this population of 10 692 females and males born between 1945 and 1973, the median reported maternal age at delivery was 28.6 years. Current asthma prevalence was 10%, asthma symptoms 23% and atopy 32% (table 1). With increasing maternal age at delivery, participants were older, less overweight, less often single- or the first-born child and less often exposed to maternal smoking in pregnancy. In the subsample of 6303 participants with data on maternal education, mothers with age at delivery between 25 and 29 years had the highest level of education (online supplementary table E1).

Maternal age and lung function

As maternal age at delivery increased, FEV_1 and FEV_1/FVC ratio increased after adjustments for age at the second survey, sex, height, maternal smoking during pregnancy and number of older siblings (table 2, fig. 1a and b). Associations with FVC were weaker and less consistent (table 2, online supplementary figure E1). No association with FEV_1 decline could be detected (figure 1a). In table 2 results are shown for males and females together, as interaction analyses did not reveal significant sex differences. In stratified analyses an association of maternal age with FEV_1 was significant only among females (p_{trend} 0.025).

There was no significant heterogeneity between countries in the association between maternal age at delivery and FEV_1 ($p_{heterogeneity}$ 0.749) (figure 2).

Sensitivity analysis

Further adjustment for maternal educational level in a subsample of 6303 participants with available data did not attenuate associations (online supplementary table E5A). In addition, the results were consistent in analyses adjusted for or stratified by number of older siblings (online supplementary tables E2A and B). Analyses with exclusion of Melbourne data were performed, and the direction of results remained unchanged (data not shown). Moreover, sensitivity analyses with further adjustments for BMI, smoking history and age difference between surveys did not change the associations (data not shown).

Maternal age and asthma and allergy phenotypes

In unadjusted analyses, the prevalence of current asthma, asthma symptoms, childhood-onset and adolescent-onset asthma decreased with increasing maternal age. Maternal age was related to asthma and asthma symptoms only in females and not in males (online supplementary table E3).

After adjustment for centre, maternal smoking in pregnancy and number of older siblings, increasing maternal age at delivery was associated with decreasing risk of current asthma, asthma symptoms and adolescent-onset asthma in females (table 3). The association was present for both atopic and non-atopic asthma outcomes. In males, no associations between maternal age at delivery and adult asthma and allergy phenotypes were observed (table 3). There was an interaction between maternal age at delivery and sex of the offspring in the associations with asthma, symptoms and asthma and symptoms with atopy (table 3). The predicted adjusted risks of asthma (figure 3a) and asthma symptoms (figure 3b) according to maternal age at delivery differed markedly according to sex: among females, the predicted risk for asthma and symptoms decreased linearly with increasing maternal age, while these risks did not vary among males.

TABLE 1 Characteristics of the study population by country

	Study population	Maternal age at delivery years	Maternal smoking in pregnancy	Maternal education level (primary school)[#]	Current asthma[¶]	Respiratory symptoms[+]	Atopy[§]	FEV_1 mL	FEV_1/FVC ratio
Melbourne, Australia	615 (5.8)	29.0 (25–33)	104 (17.0)	212 (57.6)	108 (17.6)	221 (35.9)	225 (53.3)	3699±834	79.3±6.6
Belgium	707 (6.6)	28.6 (24–32)	62 (8.9)	150 (45.5)	35 (5.0)	116 (16.6)	171 (31.2)	3705±799	80.7±6.2
Estonia	326 (3.1)	28.3 (24–33)	6 (1.9)	101 (53.7)	6 (1.8)	66 (20.3)	66 (22.5)	3788±931	82.9±7.5
France	1198 (11.2)	28.8 (24–33)	40 (3.4)	549 (59.2)	100 (8.4)	207 (17.6)	304 (33.7)	3382±779	82.6±7.3
Germany	577 (5.4)	27.4 (23–31)	27 (4.8)	255 (64.7)	28 (4.9)	89 (15.4)	163 (30.2)	3695±813	80.4±6.1
Iceland	522 (4.9)	27.5 (22–33)	92 (17.9)	250 (65.3)	41 (7.9)	86 (16.6)	85 (16.8)	3427±776	79.6±7.3
Italy	588 (5.5)	29.0 (25–33)	27 (4.8)	258 (71.3)	33 (5.6)	78 (13.4)	133 (29.6)	3457±812	81.4±6.3
The Netherlands	150 (1.4)	29.8 (25–34)	20 (13.6)	2 (28.6)	7 (4.7)	26 (17.3)			
Norway	588 (5.5)	28.7 (24–33)	83 (14.2)	239 (61.4)	42 (7.2)	115 (20.6)	138 (25.1)	3437±791	77.7±5.7
Spain	1856 (17.4)	29.7 (25–33)	22 (1.2)	901 (74.7)	147 (7.9)	495 (26.8)	369 (25.6)	3364±818	80.1±7.0
Sweden	1832 (17.1)	28.1 (23–32)	286 (15.8)	740 (64.1)	293 (16.2)	454 (25.4)	413 (33.4)	3621±798	80±7.1
Switzerland	549 (5.1)	28.9 (25–33)	23 (4.2)	113 (63.1)	63 (11.5)	115 (21.2)	200 (43.7)	3564±870	78.4±7.3
UK	955 (8.9)	27.6 (23–31)	204 (22.0)	246 (63.9)	186 (19.5)	312 (33.5)	329 (42.7)	3217±809	79±7.0
Portland, USA	229 (2.1)	27.3 (23–31)	61 (27.4)	10 (34.5)	22 (9.7)	49 (21.9)	67 (39.6)	3289±705	78.3±5.7
Total	10 692 (100)	28.6 (24–33)	1057 (10.0)	4026 (63.9)	1111 (10.4)	2429 (23.0)	2663 (32.2)	3488±825	80.1±7.0

Data are presented as n (%), median (interquartile range) or mean±SD. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: available for subsample of 6303 participants; [¶]: current asthma medication and/or asthma attacks in past 12 months; [+]: three or more of the following symptoms in past 12 months: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in chest, shortness of breath in daytime, shortness of breath after strenuous activity, waking by shortness of breath or waking by attack of cough; [§]: serum IgE >0.35 $kU \cdot L^{-1}$ for *Dermatophagoides pteronyssinus*, cat dander, timothy grass and/or *Cladosporium herbarum*.

Sensitivity analysis

Additional adjustment for maternal educational level in a subsample of 6303 participants with available data did not attenuate these associations (online supplementary table E5A). This was further supported by a likelihood ratio test with and without maternal education that did not show a difference in results for asthma ($p=0.48$) or symptoms ($p=0.1$) (data not shown).

Analyses were stratified by being single child or not; for most outcomes, interactions between being a single child and maternal age were not present (online supplementary table E4). A three-way interaction between maternal age, sex and being a single child was not significant ($p_{interaction}=0.656$). Adjustment for number of older siblings or analyses stratified by number of older siblings showed consistent results (online supplementary tables E5A and B).

Additional adjustment for offspring's age and BMI, daycare attendance before age 5 years, living environment in early childhood and maternal asthma, in addition to the basic adjustments (centre,

TABLE 2 Associations of maternal age at delivery (continuous, per 5-year increase) with forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio and FEV_1 decline with adjustments for age at the second survey, sex, height, maternal smoking during pregnancy and number of older siblings

	Adjusted coefficient[#] β (95% CI)	Intercept[¶]
FEV_1 mL	11.66 (1.71–21.61)	4265
FVC mL	5.42 (−5.80–16.63)	5294
FEV_1/FVC %	0.19 (0.05–0.32)	81
FEV_1 decline mL[§]	1.73 (−4.26–7.72)	277

n=12 421. [#]: per 5-year increase in maternal age at delivery after age 14 years in an adjusted multilevel linear mixed model with centre as a random intercepts and adjustments for age at the second survey, sex, height, maternal smoking during pregnancy and number of older siblings; [¶]: centred at maternal age at delivery of 14 years; [§]: decline in FEV_1 in mL per year of follow-up (FEV_1 in European Community Respiratory Health Survey (ECRHS) I minus FEV_1 in ECRHS II; a positive value represents decline).

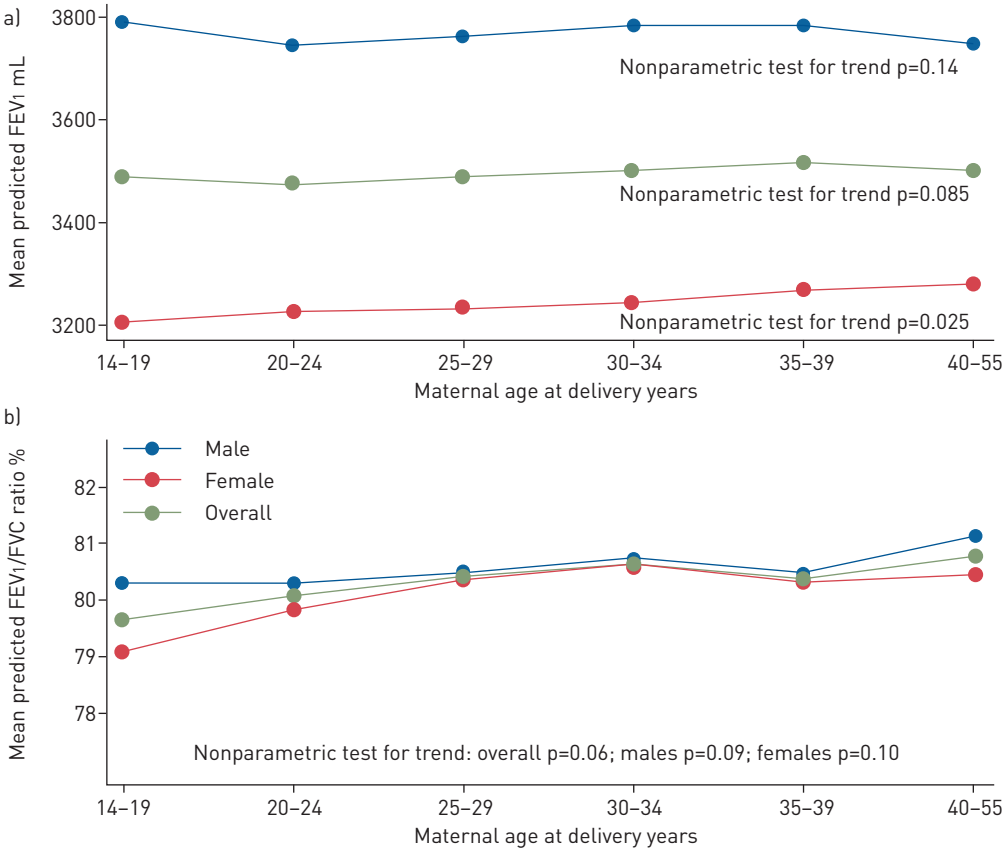

FIGURE 1 Maternal age at delivery as associated with a) forced expiratory volume in 1 s (FEV_1) and sex of the child, and b) FEV_1/forced expiratory volume (FVC) ratio from adjusted mixed model with country and centre as a random intercept.

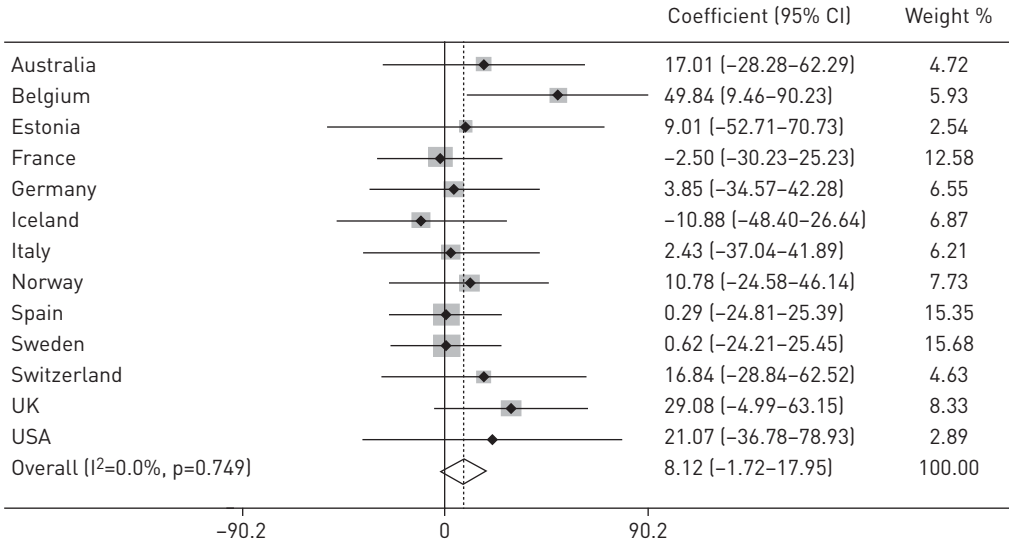

FIGURE 2 Coefficients for the association between maternal age at delivery and forced expiratory volume in 1 s, by country. Adjustment within country for age, height, sex, maternal smoking in pregnancy, single child or not and number of older siblings. For each country, horizontal line indicates the 95% confidence interval. For the overall estimates, the diamond indicates coefficient with 95% confidence interval. The size of each square is proportional to the sample size. Coefficients are per 5-year increase.

TABLE 3 Associations of maternal age at delivery (per 5-year increase) with asthma and allergy phenotypes, stratified by sex

	Males	Females	$p_{interaction}$ for sex[#]
Subjects n	4996	5696	
Current asthma[¶]	1.04 (0.95–1.14)	**0.85 (0.79–0.92)**	0.050
Asthma symptoms[+]	1.02 (0.96–1.09)	**0.87 (0.82–0.92)**	0.001
Childhood asthma[§]	0.98 (0.88–1.09)	0.96 (0.85–1.07)	0.7
Adolescent asthma[f]	0.98 (0.84–1.13)	**0.89 (0.79–0.99)**	0.180
Hay fever	1.05 (0.99–1.11)	1.03 (0.98–1.08)	0.3
Atopic and non-atopic outcomes			
Asthma[+] with atopy[##]	1.01 (0.9–1.14)	**0.81 (0.72–0.93)**	0.100
Asthma[+] without atopy[##]	0.98 (0.79–1.22)	**0.86 (0.75–0.97)**	0.4
Symptoms[+] with atopy[##]	1.03 (0.93–1.15)	**0.81 (0.73–0.91)**	0.001
Symptoms[+] without atopy[##]	1.00 (0.91–1.11)	**0.91 (0.84–0.98)**	0.140

Data are presented as OR (95% CI), adjusted for centre, maternal smoking in pregnancy and number of older siblings, unless otherwise stated. Associations with OR (95% CI) <1.0 are presented in bold. [#]: p-value for interaction term of sex with maternal age in 5-year categories; [¶]: current asthma medication and/or asthma attacks in past 12 months; [+]: three or more of the following symptoms in past 12 months: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in chest, shortness of breath in daytime, shortness of breath after strenuous activity, waking by shortness of breath or waking by attack of cough; [§]: onset at age ⩽10 years; [f]: onset at age >10 years and <20 years; [##]: serum IgE >0.35 $kU \cdot L^{-1}$ for *Dermatophagoides pteronyssinus*, cat dander, timothy grass and/or *Cladosporium herbarum*.

maternal smoking in pregnancy, number of older siblings and maternal educational level) strengthened rather than attenuated the associations (current asthma: males OR 1.08 (95% CI 0.94–1.25), females OR 0.80 (95% CI 0.70–0.92); asthma symptoms: males OR 1.09 (95% CI 0.99–1.20), females OR 0.80 (95% CI 0.80–0.96)). Further adjustments for birthweight in a subsample (n=2183) did not change the estimates (data not shown). Sensitivity analyses restricted to those reporting maternal age at delivery >20 and <40 years, and with adjustments for all the previously mentioned factors did not change the associations (current asthma: males OR 0.99 (95% CI 0.82–1.19), females OR 0.77 (95% CI 0.65–0.92); asthma symptoms: males OR 1.08 (95% CI 0.96–1.22), females OR 0.85 (95% CI 0.76–0.95)).

There was no heterogeneity among countries in the association between maternal age at delivery and asthma symptoms among females ($p_{heterogeneity}$=0.801) (figure 4a) or males ($p_{heterogeneity}$=0.449) (figure 4b). Results were similar for current asthma (data not shown).

Validation study

A validation study included 329 participants from Bergen born 1967–1971 with data from the Norwegian medical birth registry. Paired t-tests showed that self-reported mother's age at delivery was not different from mother's age recorded in the birth registry; this was true both for male and female offspring (difference (95% CI) 0.19 (−0.15–0.52) years; males 0.28 (−0.17–0.73) years, females 0.12 (–0.37–0.59) years; range 17–45 years for both measures).

Discussion

In this analysis of a large multinational cohort increasing maternal age did not appear to impact negatively on offspring's adult respiratory health. Higher maternal age at delivery was related to increasing levels of FEV_1 and higher FEV_1/FVC ratio in the offspring, possibly more pronounced among females. Moreover, increasing maternal age at delivery was related to decreasing risk of asthma and asthma symptoms among female offspring, while these associations were not present among male offspring. The results were robust across countries with different sociocultural characteristics, and with adjustment for a range of factors (maternal smoking, asthma and educational level; and offspring number of older siblings, single child, number of siblings, birth weight, age, BMI, daycare attendance before 5 years of age and living environment in early childhood).

The impact of maternal age on lung function is a novel finding. It is of interest that effects were observed for FEV_1 and FEV_1/ FVC ratio rather than FVC, suggesting an effect on airways obstruction. The association with an obstructive spirometric pattern is consistent with findings for asthma and respiratory symptoms. An inverse relationship between maternal age at delivery and adult risk of asthma and respiratory symptoms in offspring is in agreement with an analyses of the RHINE (Respiratory Health in

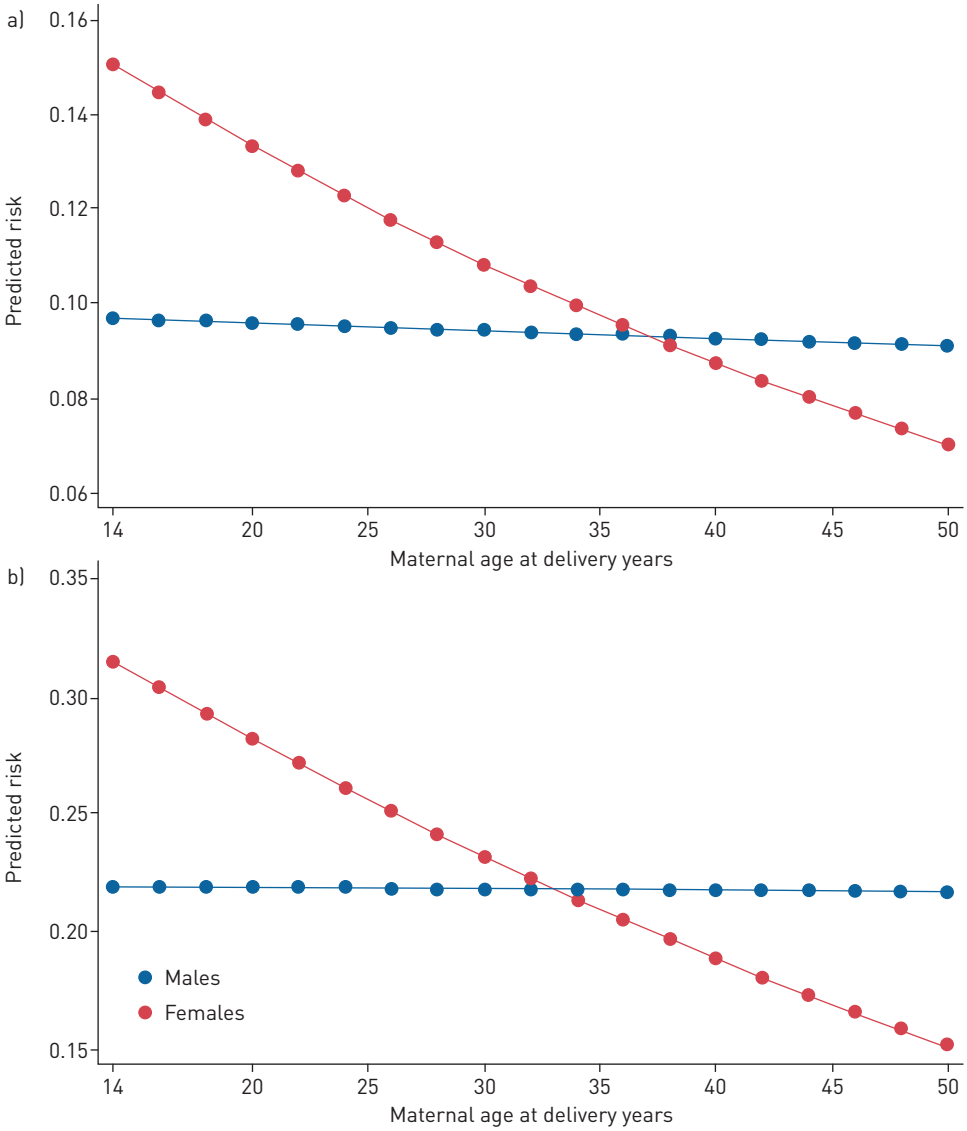

FIGURE 3 Predicted risk of a) asthma and b) three or more asthma symptoms, according to maternal age at delivery by sex, with adjustment for centre, maternal smoking in pregnancy and number of older siblings.

Northern Europe) questionnaire study in Northern Europe [6], with a Swedish study of conscripts [19], and with an analysis using birth characteristics data from the Norwegian medical birth registry for Bergen ECRHS I subsample aged 20–25 years [20]. The observed sex difference in the relationship between maternal age and asthma is to our knowledge a novel finding.

The present study could not identify an association between maternal age and lung function decline, while a previous analysis of the ECRHS and the SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults) cohorts analysed together found accelerated lung function decline in persons with maternal age >31 years [9]. Our analysis included a considerably smaller number of subjects and thus had less power to detect an association than the study by Dratva *et al.* [9]. At first glance, the observation of higher lung function with increasing maternal age may seem to contradict a previous study showing accelerated lung function decline in persons born to mothers in the oldest 50 percentile [9]. However, attained lung function level, related to growth and development of the lungs, expresses a different aspect of respiratory health than decline in lung function, reflecting lung ageing. Thus, it seems reasonable that maternal ageing could have different biological effects on these two outcomes. These differences might prove useful to future research on the biological mechanisms related to maternal ageing effects in offspring.

The findings are biologically plausible in the sense that maternal age effects are described for a variety of health outcomes in offspring, and in the sense that sex-specific effects were observed. However, the direction of effects, with improving lung function and respiratory health with maternal ageing, seems

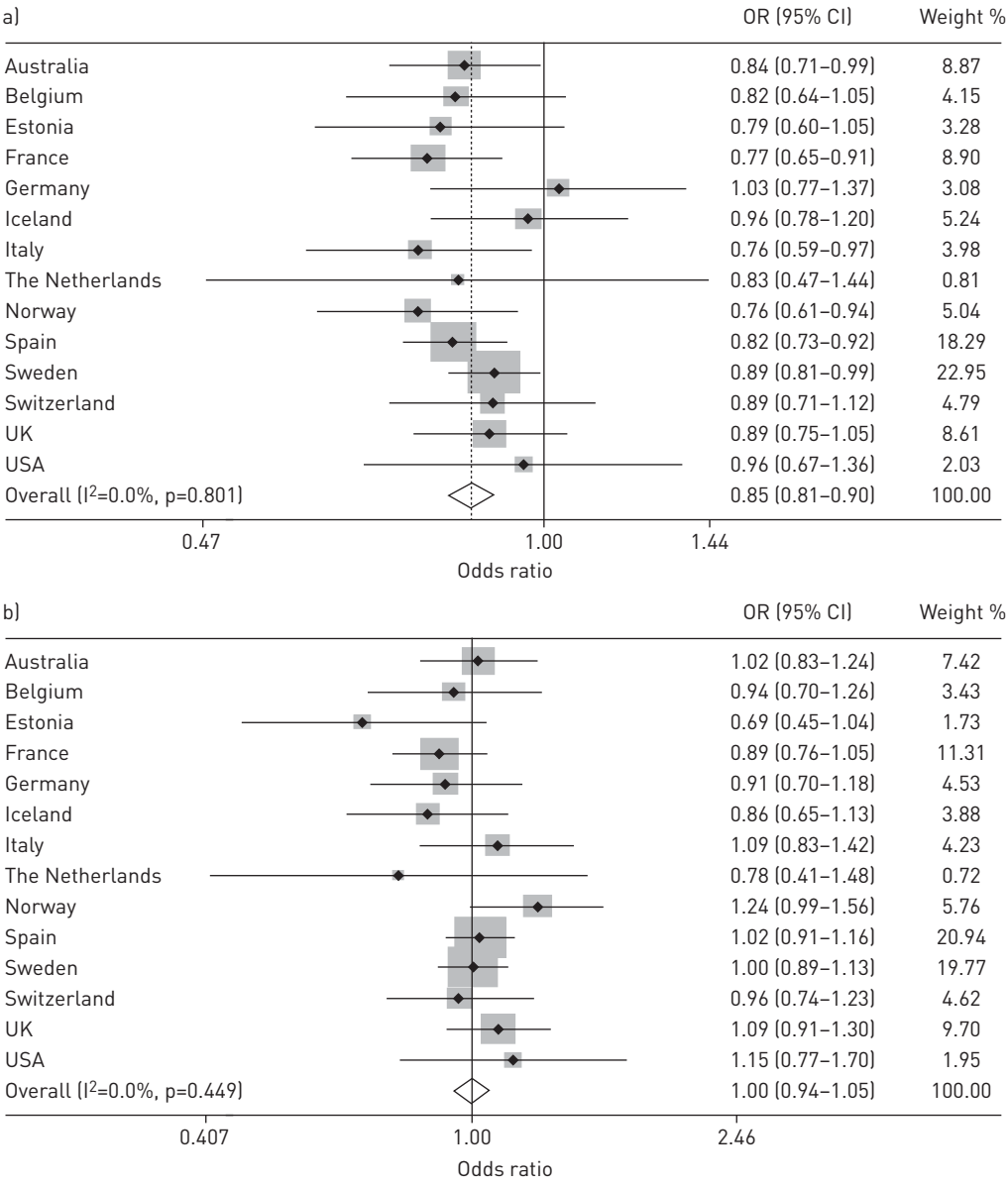

FIGURE 4 Meta-analysis showing odds ratios for the association between maternal age at delivery and asthma symptoms by country, in a) females and b) males. Adjustment within country for maternal smoking in pregnancy and number of older siblings. For each country, horizontal line indicates the 95% confidence interval. For the overall estimates, the diamond indicates OR (95% CI). The size of each square is proportional to the sample size. Odds ratios are per 5-year increase.

contra-intuitive. It is well known that short-term pregnancy outcomes are poorer in older mothers, and new research suggests increased methylation in the placenta with increasing maternal age [21]. There is a possibility of unknown confounding, as discussed in more detail below, such as social conditions and lifestyle both of mothers and offspring, or older mothers taking better care of their infants [14]. However, the consistency of the findings after extensive adjustments for maternal, early childhood, and adult factors; across countries in three continents differing widely in language, socioeconomic status, education and health systems; and for an outcome of measured adult lung function decades after birth, advocate further research into potential underlying biological mechanisms.

We might question whether maternal age might influence offspring respiratory health through long-term effects of adverse pregnancy outcomes [22, 23], which often have a sexual dimorphism with detrimental effects on the male fetus [24]. However, adverse obstetrical and perinatal outcomes are more frequent both among young [11, 25, 26] and old mothers [12, 27, 28], and our analyses revealed linear, not U-shaped, patterns in the associations of maternal age with FEV_1 and asthma symptoms (figures 1a and 3b).

Furthermore, our results were not driven by maternal age <20 years or >40 years, as exclusion of these groups showed unaltered results.

We might further speculate whether pre-conception factors related to older age of the mother, such as metabolic, hormonal or immunologic status, might affect the offspring *via* transmissible epigenetic changes. There may be several sex-specific mechanisms that may explain the observed sex differences. There is evidence that maternal age is related to growth in the placenta [29, 30] and fetus [10, 31], and that sex-specific epigenetic changes related to maternal nutrition [32, 33] are transmitted to the next generation [34]. Such changes may determine early placental programming and differ according to fetal sex [35], affect fetal organ growth [36] and potentially adult health and disease [34]. The placenta may react differently to the same environment depending on the sex of the fetus [35], thus an adult phenotype may already be partly shaped *in utero*. Possibly, epigenetic changes and early programming in pregnancy associated with maternal age [21, 37, 38] might explain the findings in this study. Furthermore, maternal age might be associated with paternal age, and thus indirectly reflect ageing effects on sperm development.

In this study the participants were born between 1945 and 1973, before assisted reproduction became widely available or available at all. Older mothers might possibly be "fertility survivors", as older females able to get naturally pregnant might represent a healthier group with healthier offspring. It seems unlikely that this could explain the observed differences according to offspring sex.

Maternal age is closely associated with parity and number of siblings. A rich literature shows associations of birth order or number of siblings with various measures of respiratory health and allergy. Mattes *et al.* [39] found that lung function in school-aged children was associated with number of siblings. Among adults in the ECRHS study asthma there was a U-shaped association with number of siblings, while hay fever and atopy showed inverse associations [40]. The present study showed that the effect of maternal age was independent of number of siblings or of number of older siblings. Further studies of family size/birth order should consider potential confounding by maternal age; it is possible that maternal age is a key factor that has confounded previous literature on family size/birth order and allergic diseases.

Strengths of the present study include the international, multicentre ECRHS cohort, with measured lung function and specific IgEs in a large study population, the possibility to investigate an early life factor in relation to well-characterised adult health outcomes, and the multicultural and population-based study design. The loss to follow-up in the ECRHS is complex, but an analysis of a daughter study of the ECRHS found that while prevalence estimates at follow-up were biased, risk-associations were not affected by loss to follow-up [41]. It seems unlikely that loss to follow-up has created the associations of maternal age with lung function and asthma; such a spurious association could only result from an opposite association in the persons who did not participate, which seems unlikely. The use of self-reported data for maternal age at delivery represents a weakness; however, a validation study suggested that reporting of maternal age was very reliable, in both males and females. Error in other self-reported variables is possible, and we might question whether there could be differential precision of recall in males and females. However, participants in population-based studies appeared to report perinatal data accurately [42], and an analysis from the ECRHS study found that adult reliability in reporting of childhood events was very good and did not differ by sex or disease status [43]. Maternal smoking is an important confounding variable, and reporting bias may be differential with regard to having a very young mother. As the findings were consistent when excluding those with maternal age <20 years, it seems unlikely that differential misclassification in maternal smoking would be of notable importance for the results. Although reporting bias in relation to self-reported asthma outcomes may be present, reporting bias is unlikely to be differential with regard to objective outcomes like measured lung function. While consistency of the results across centres, with different adjustments and by different ways of analyses, speaks against a major role of residual confounding, residual confounding by behavioural factors related to maternal age cannot be ruled out. Comprehensive data on pregnancy outcomes and complications were not available, beyond birthweight data for >2000 participants from Northern Europe.

Conclusions

In a large multicentre population-based study, increasing maternal age at delivery was related to a higher level of lung function and lower risk of asthma and respiratory symptoms, but only among females. The results were consistent after adjustment for a range of potential confounders, and across countries with different sociocultural characteristics. The present findings are relevant and reassuring with regard to respiratory health effects of the ongoing demographic changes with increasing maternal age. The biological mechanisms underlying the observed sex-specific effects of maternal ageing should be investigated further. Potential impact of assisted reproduction and pregnancy complications in relation to maternal ageing is an open question that should be addressed in younger birth cohorts.

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