

ONLINE DATA SUPPLEMENT

Maternal Age at Delivery, Lung Function and Asthma in Adult Offspring: a Population-based Survey

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METHODS

Study design and participants

ECRHS I(1) is an international survey carried out in 1992-1994 that recruited randomly selected individuals aged 20-44 years from general populations within administrative boundaries of 36 centres in 16 countries. A random sample and a symptomatic sample were invited to a follow-up study, ECRHS II(2), which took place in 1998-2002. The examinations carried out at both surveys included an interviewer-led questionnaire, lung function measurements, and blood samples for measurement of serum specific IgEs. The study is described in detail at www.ecrhs.org. Complete data was available for 10,692 participants. Additional data were available on maternal educational level for 6,303 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 1967-71 from Bergen.

Ethical approval was obtained for each study centre from the appropriate institutional or regional ethics committee, and each participant provided informed written consent.

Maternal age

Maternal age at delivery was assessed by the question “How old was your mother when you were born?”

Outcomes variables

Current asthma was defined as answering yes to the questions “Have you had an attack of asthma in the last 12 months?”, “Are you currently taking any asthma medicines?”, or both.

Childhood-onset asthma was defined as answering yes to “Have you ever had asthma?” and answering 10 years or younger to “How old were you when you had your first attack of asthma?”

Adolescent-onset asthma was defined as answering yes to “Have you ever had asthma?” and answering older than 10 and younger than 21 years to “How old were you when you had your first attack of asthma?”

Asthma symptoms were defined as the presence of 3 or more of the following symptoms during the last 12 months: wheeze, wheeze with shortness of breath, wheeze when not having a cold, waking with tightness in the chest, shortness of breath at rest in daytime, shortness of breath after strenuous activity, waking with shortness of breath, waking with an attack of cough(3).

Hay fever was defined as answering yes to the question “Do you have any nasal allergies, including hay fever?”

Atopy was defined as sensitization to at least one of four specific allergens [house dust mite (*Dermatophagoides pteronyssinus*), cat dander (*Fel D1*), timothy grass, *Cladosporium herbarum*] as measured by a serum IgE antibody level higher than 0.35 kU/L, using the Pharmacia CAP system (Pharmacia Diagnostic AB, Uppsala, Sweden)

Asthma with atopy was defined as the presence of both current asthma and atopy; *current asthma without atopy* as current asthma and no atopy; *asthma symptoms with atopy* as both asthma symptoms and atopy; and *asthma symptoms without atopy* as asthma symptoms and no atopy.

Lung function was measured using a standard spirometric method described previously(4).

The maximum *forced expiratory volume in one second (FEV₁)* and maximum *forced vital capacity (FVC)* of up to five technically acceptable manoeuvres were determined. *Decline in FEV₁* was expressed as ECRHS I value minus ECRHS II value per year of follow-up (a positive value represents decline). Twenty-two centres used the same spirometer in ECRHS I and II, mostly with updated software at the second occasion. Two centres used SensorMedics dry spirometer at one occasion, Jaeger Masterscope at the other. Two used Jaeger Pneumotach at each survey, but not the same instrument. A fifth used SensorMedics spirometer and SensorMedics Vmax 22. One centre (Melbourne) used Pneumotach in ECRHS I, and a rolling seal spirometer (Sensor-Medics, Yorba Linda, California, USA) in ECRHS II. Differences in spirometric equipment between centres were accounted for in the statistical analyses of the data.

Height and *weight* were measured by a field worker during the ECRHS II clinical visit before measurement of lung function.

Covariates

BMI was calculated based on the measured height and weight.

Number of older siblings was determined using the information from the ECRHS I questions on “How many older brothers do or did you have?” and “How many older sisters do or did you have?”

Being a *single child* was defined by answering 0 to both these questions.

Maternal smoking in pregnancy was defined by answering yes to the questions “Did your mother ever smoke regularly during your childhood, or before you were born?” and “Did your mother smoke as usual during pregnancy?”

Maternal educational level was defined by answers to the question “What was the highest level of education your mother had?” that included the alternate answers: “Up to the minimum school leaving age”, “Secondary school/technical school past the minimum age” and “College or University”

Maternal asthma was defined by answering yes to the question “Did your mother ever have asthma?”

Day-care attendance was defined by answering yes to the question “Did you go to a school, play-school or nursery with older children before the age of five years?”

Living environment in early childhood was defined by answers to the question “What term best describes the place you lived most of the time when you were under the age of five years?” that included the alternate answers: “farm”, “village in rural area”, “small town”, “suburb of a city” and “inner city”

Statistical analyses

Due to the complexity of potential interrelated causal pathways, a directed acyclic graph (DAG) for the relationship between maternal age and offspring respiratory health was constructed. The DAG included centre, maternal smoking in pregnancy, fertility, parity, maternal obesity and maternal educational level in addition to maternal age at delivery and respiratory outcomes. In order to identify minimally sufficient adjustment (MSA) sets, the model was analysed using the DAGitty software, version 2014-10-30(5). The identified MSA set included centre, maternal educational level, birth order (as proxy for parity and for fertility).

Maternal age was analysed either as a categorical variable with six classes centred at age 14 years and split into 5-year age groups with values of 40 and over collapsed into one group; or as a continuous variable ranging from 14 to 55 years. Non-parametric test for trend across ordered groups was used to identify differences according to maternal age in categories.

Multilevel mixed-effects logistic regressions were used to assess the association between maternal age at delivery (per 5 years 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. Multilevel mixed models with centre as a random intercept were used to assess the associations of maternal age with the lung function outcomes FEV₁, FVC and FEV₁/FVC ratio (%), with adjustments for age at ECRHS II, sex, height, maternal smoking during pregnancy and number of older siblings. For analyses of lung function, maternal age was used either as a continuous variable (overall associations) or as a categorical (predicted levels of lung function stratified by sex). Centre was entered as a random intercept in the models due to the change of spirometers between ECRHS I and II. For the same reason, sensitivity analyses were performed with exclusion of participants from Melbourne.

Differences between subgroups were analysed by means of stratified logistic regression models and by including interaction terms of maternal age with sex, or being a single child, in analyses of respiratory symptoms and lung function. Sensitivity analyses with additional adjustment for maternal educational level were performed using the available data for the subsample taking part in the latest follow-up of the cohort in analyses of respiratory symptoms and lung function.

In analyses of asthma and symptoms, additional sensitivity analyses with further adjustments for offspring's age and BMI, day care attendance before 5 years of age, living environment in early childhood, and maternal asthma were performed, and restricted to those reporting maternal age at delivery over 20 and under 40 years, and with adjustments for all the previously mentioned factors.

In analyses of lung function, additional sensitivity analyses with further adjustments for BMI, smoking history and age difference between surveys, and with exclusion of Melbourne, were performed.

Potential heterogeneity between centres was studied by random-effects meta-analyses.

All the analyses were performed using STATA13 (Stata Corp, College Station, Texas).

TABLE E1. Adult and early life characteristics according to maternal age at delivery

Maternal age (years)	All (n=10692)	14-19 (n=462)	20-24 (n=2566)	25-29 (n=3135)	30-34 (n=2624)	35-39 (n=1328)	40-55 (n=577)	p-value *
Adult characteristics								
Age , yrs., median (IQR)	42 (36-48)	41 (36-47)	41 (35-48)	42 (36-48)	43 (37-48)	43 (37-49)	45 (38-50)	0.0001
Height , m, mean (SD)	1.70 (0.1)	1.70 (0.1)	1.71 (0.1)	1.70 (0.1)	1.70 (0.1)	1.70 (0.1)	1.70 (0.1)	0.3
BMI , mean (SD)	25.7 (4.6)	26.6 (5.3)	25.9 (4.7)	25.5 (4.4)	25.6 (4.5)	25.8 (5)	25.4 (4.3)	0.001
Smoking , current, n (%)	3095 (29.0)	143 (31.0)	743 (29.0)	851 (27.2)	785 (29.9)	395 (29.7)	178 (30.9)	<0.0001
Early life characteristics								
Single child , n (%)	1034 (9.7)	79 (17.3)	292 (11.4)	262 (8.4)	234 (8.9)	113 (8.5)	54 (9.4)	<0.0001
Number of older siblings								<0.0001
None, n (%)	4330 (40.5)	405 (87.7)	1679 (65.4)	1312 (41.9)	651 (24.8)	211 (15.9)	72 (12.5)	
One, n (%)	3133 (29.3)	47 (10)	676 (26.3)	1130 (36)	862 (32.9)	335 (25.2)	84 (14.6)	
Two or more, n (%)	3229 (30.2)	11 (2.4)	211 (8.2)	693 (22.1)	1111 (42.3)	782 (59.0)	421 (73.0)	
Maternal smoking in pregnancy , n (%)	1057 (10.0)	76 (17.0)	326 (12.9)	299 (9.6)	230 (8.9)	92 (7).0	34 (6.0)	<0.0001
Maternal education †								<0.0001
Primary school, n (%)	4026 (63.9)	173 (67.3)	947 (63.9)	1098 (60.0)	1048 (65.6)	505 (64.0)	255 (73.1)	
Secondary school, n (%)	1438 (22.8)	61 (23.7)	361 (24.3)	459 (25.1)	326 (20.4)	175 (22.2)	56 (16.1)	
College or university, n (%)	751(11.9)	16 (6.3)	159 (10.7)	251 (13.7)	197 (12.3)	97 (12.3)	31 (8.9)	

* p-value based on nonparametric test for trend across ordered groups

† Available for subsample of 6303 participants

Table E2A Associations of maternal age at delivery with FEV₁, FVC and FEV₁/FVC ratio, and FEV₁ decline, with adjustments for age at the second survey, sex, height, maternal smoking during pregnancy, and additional adjustment for number of older siblings.

	Adjusted coefficient*	95% CI	Intercept[‡]
	β		
FEV₁, mL	10.40	0.05; 20.4	4262
FVC, mL	4.60	-6.70; 15.75	5295
FEV₁/FVC, %	0.15	0.05; 0.30	81
FEV₁ decline, mL[§]	1.65	-4.35; 7.65	273

* Per 5 years increase in maternal age at delivery after age 14 in an adjusted multilevel 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 14 years of maternal age at delivery

[§] Decline in forced expiratory volume in one second in mL per year of follow-up (FEV₁ in ECRHS I minus FEV₁ in ECRHS II, a positive value represents decline)

Table E2B Associations of maternal age at delivery (continuous) with FEV₁ stratified by number of older siblings, with adjustments for age at the second survey, sex, height and maternal smoking during pregnancy

	Adjusted coefficient*	95% CI	p-value
	β		
FEV₁, mL			
0 siblings	11.0	-10.2; 32.1	0.31
1 sibling	15.8	1.2; 30.4	0.03
2 siblings	8.4	-5.7; 22.4	0.24
>2 siblings	15.9	4.6; 27.2	0.006

* Per 5 years increase in maternal age at delivery after age 14 in an adjusted multilevel mixed model with centre as a random intercepts and adjustments for age at the second survey, sex, height and maternal smoking during pregnancy

TABLE E3. Prevalence of asthma and allergy phenotypes according to maternal age at delivery

	Maternal age at delivery (years)								<i>P</i> -trend*	<i>P</i> -interaction for gender
		<i>All</i> (<i>n</i> =10692)	14-19 (<i>n</i> =462)	20-24 (<i>n</i> =2566)	25-29 (<i>n</i> =3135)	30-34 (<i>n</i> =2624)	35-39 (<i>n</i> =1328)	40-55 (<i>n</i> =577)		
Current asthma [†] (%)	Male	9.4	10.5	9.3	9.0	9.5	9.1	10.8	<i>p</i> =0.79	0.028
	Female	11.4	16.3	12.1	11.5	11.4	8.9	9.1	<i>p</i>=0.002	
Asthma symptoms [‡] (%)	Male	21.7	20.3	21.7	21.5	21.5	22.2	24.3	<i>p</i> =0.41	0.001
	Female	24.2	33.2	26.5	23.9	22.6	21.9	20.6	<i>P</i><0.0001	
Childhood asthma [§] (%)	Male	6.4	5.4	7.0	6.9	6.2	4.4	6.3	<i>p</i> =0.16	0.66
	Female	4.8	7.0	5.1	5.0	4.0	4.1	4.6	<i>p</i> =0.055	
Adolescent asthma (%)	Male	3.4	5.9	2.7	3.7	3.0	3.2	4.4	<i>p</i> =1	0.19
	Female	4.8	5.0	5.9	4.4	5.3	3.2	3.6	<i>p</i>=0.035	
Hay fever (%)	Male	30.1	29.4	29.6	32.3	27.2	30.6	33.0	<i>p</i> =0.97	0.37
	Female	34.9	42.0	35.2	34.1	35.1	32.4	36.5	<i>p</i> =0.2	
Asthma [†] with atopy ^{**} (%)	Male	7.4	6.3	7.9	7.4	7.0	6.8	10.1	<i>p</i> =0.91	0.029
	Female	6.8	10.0	7.4	7.7	6.1	4.9	3.8	<i>p</i>=0.002	
Asthma [†] without atopy ^{**} (%)	Male	2.0	4.4	2.1	1.2	2.5	2.6	0.9	<i>p</i> =0.7	0.81
	Female	5.1	5.9	5.3	4.7	5.7	4.7	3.4	<i>p</i> =0.28	
Symptoms [‡] with atopy ^{**} (%)	Male	11.9	5.6	11.7	12.7	11.5	12.5	14.4	<i>p</i> =0.25	0.001
	Female	10.3	13.7	11.5	11.7	9.0	7.9	6.8	<i>p</i><0.0001	
Symptoms [‡] without atopy ^{**} (%)	Male	10.0	12.5	10.2	9.4	10.7	11.5	9.7	<i>p</i> =0.57	0.22
	Female	15.0	18.7	15.7	13.0	14.3	15.6	13.7	<i>p</i> =0.21	

* *P*-value based on nonparametric test for trend across ordered groups

† Current asthma medication and/or asthma attacks last 12 months

‡ ≥3 of the following symptoms last 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, waking by attack of cough

§ Onset ≤10 years

|| Onset >10 years and <20 years

** Serum IgE >0.35 kU/L for *Dermatophagoides pteronyssinus*, cat dander, timothy grass and/or *Cladosporium herbarum*

TABLE E4. Associations of maternal age at delivery (per 5 years increase) with asthma and allergy phenotypes stratified by sex and being single child or not*

	Males (n=4996)			Females (n=5696)		
	Not a single child (n= 4472) OR † (95%CI)	Single child (n= 504) OR † (95%CI)	<i>p</i> -interaction for being a single child or not among males ‡	Not a single child (n= 5142) OR † (95%CI)	Single child (n= 530) OR † (95%CI)	<i>p</i> -interaction for being a single child or not among females ‡
Current asthma [§]	1.07 (0.97-1.18)	0.86 (0.67-1.10)	0.145	0.85 (0.78-0.92)	0.80 (0.64-0.99)	0.3
Asthma symptoms	1.03 (0.96-1.10)	0.97 (0.81-1.15)	0.7	0.87 (0.81-0.92)	0.81 (0.68-0.96)	0.133
Childhood asthma ^{**}	0.98 (0.87-1.11)	0.90 (0.69-1.17)	0.9	0.98 (0.86-1.11)	0.76 (0.57-1.02)	0.4
Adolescent asthma ^{††}	0.98 (0.84-1.14)	1.11 (0.71-1.76)	0.5	0.85 (0.75-0.96)	1.08 (0.80-1.46)	0.196
Hay fever	1.07 (1.00-1.14)	0.94 (0.81-1.09)	0.3	1.02 (0.97-1.08)	1.00 (0.87-1.15)	0.9
<i>Atopic and non-atopic outcomes</i>						
Asthma [§] with atopy ^{‡‡}	1.03 (0.90-1.18)	0.89 (0.66-1.21)	0.4	0.78 (0.67-0.90)	0.96 (0.70-1.32)	0.5
Asthma [§] with no atopy ^{‡‡}	1.04 (0.83-1.31)	0.42 (0.12-1.54)	0.071	0.86 (0.75-0.99)	0.69 (0.46-1.04)	0.2
Symptoms with atopy ^{‡‡}	1.04 (0.93-1.16)	1.00 (0.77-1.29)	0.8	0.79 (0.70-0.90)	0.83 (0.62-1.11)	0.8
Symptoms with no atopy ^{‡‡}	1.01 (0.91-1.13)	0.95 (0.70-1.29)	0.7	0.92 (0.84-1.00)	0.78 (0.60-1.02)	0.038

* Not present 3-ways interaction between maternal age, sex and being a single child (p=0.656)

† Adjusted for centre, maternal smoking in pregnancy and number of older siblings (among those not being single child)

‡ P-value for interaction term of being single child or not among males or females

§ Current asthma medication and/or asthma attacks last 12 months

|| ≥3 of the following symptoms last 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, waking by attack of cough

** Onset ≤10 years

†† Onset >10 years and <20 years

‡‡ Serum IgE >0.35 kU/L for *Dermatophagoides pteronyssinus*, cat dander, timothy grass and/or *Cladosporium herbarum*

Table E5A Associations of maternal age at delivery (per 5 years increase) with asthma and allergy phenotypes, stratified by sex, adjusted for number of older siblings

	Males (n=4996) <i>OR</i> [*] (95%CI)	Females (n= 5696) <i>OR</i> [*] (95%CI)
Current asthma [‡]	1.02 (0.95-1.09)	0.88 (0.83-0.93)
Asthma symptoms [§]	1.00 (0.96-1.05)	0.90 (0.86-0.94)
Childhood asthma	0.95 (0.88-1.03)	0.94 (0.87-1.03)
Adolescent asthma ^{**}	1.04 (0.93-1.16)	0.93 (0.85-1.01)
Hay fever	1.01 (0.97-1.06)	0.99 (0.95-1.02)
<i>Atopic and non-atopic outcomes</i>		
Asthma [‡] with atopy ^{††}	1.00 (0.91-1.09)	0.82 (0.74-0.90)
Asthma [‡] without atopy ^{††}	0.93 (0.79-1.09)	0.93 (0.84-1.02)
Symptoms [§] with atopy ^{††}	1.03 (0.95-1.11)	0.82 (0.75-0.89)
Symptoms [§] without atopy ^{††}	1.00 (0.92-1.07)	0.94 (0.89-1.00)
Additional adjustment for maternal education		
	(n=2989)	(n= 3314)
Current asthma [‡]	1.06 (0.95-1.20)	0.85 (0.77-0.94)
Asthma symptoms [§]	1.08 (0.99-1.16)	0.88 (0.82-0.95)
Childhood asthma	0.95 (0.83-1.09)	1.05 (0.91-1.21)
Adolescent asthma ^{**}	1.14 (0.94-1.40)	0.93 (0.80-1.08)
Hay fever	1.03 (0.96-1.10)	1.00 (0.94-1.06)
<i>Atopic and non-atopic outcomes</i>		
Asthma [‡] with atopy ^{††}	1.07 (0.92-1.24)	0.87 (0.74-1.03)
Asthma [‡] without atopy ^{††}	0.87 (0.64-1.16)	0.87 (0.74-1.03)
Symptoms [§] with atopy ^{††}	1.15 (1.01-1.30)	0.84 (0.73-0.96)
Symptoms [§] without atopy ^{††}	1.03 (0.91-1.15)	0.96 (0.87-1.06)

* Adjusted for centre, maternal smoking in pregnancy and number of older siblings

† P-value for interaction term of sex with maternal age in 5 years categories

‡ Current asthma medication and/or asthma attacks last 12 months

§ ≥3 of the following symptoms last 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, waking by attack of cough

|| Onset ≤10 years

** Onset >10 years and <20 years

†† Serum IgE >0.35 kU/L for *Dermatophagoides pteronyssinus*, cat dander, timothy grass and/or *Cladosporium herbarum*

Table E5B. Associations of maternal age at delivery (per 5 years increase) with asthma and asthma symptoms, among females and stratified by number of older siblings

	Current asthma <i>OR</i> [*] (95%CI)	Asthma symptoms <i>OR</i> [*] (95%CI)
NUMBER OF OLDER SIBLINGS		
0	0.74 (0.61-0.89)	0.81 (0.70-0.94)
1	0.88 (0.79-0.99)	0.84 (0.77-0.92)
2	0.91 (0.80-1.02)	0.94 (0.86-1.02)
>2	0.89 (0.82-0.98)	0.94 (0.88-0.99)

* Adjusted for centre, maternal smoking in pregnancy

Figure E1. Maternal age at delivery and FVC from an adjusted mixed model with country and centre as a random intercepts

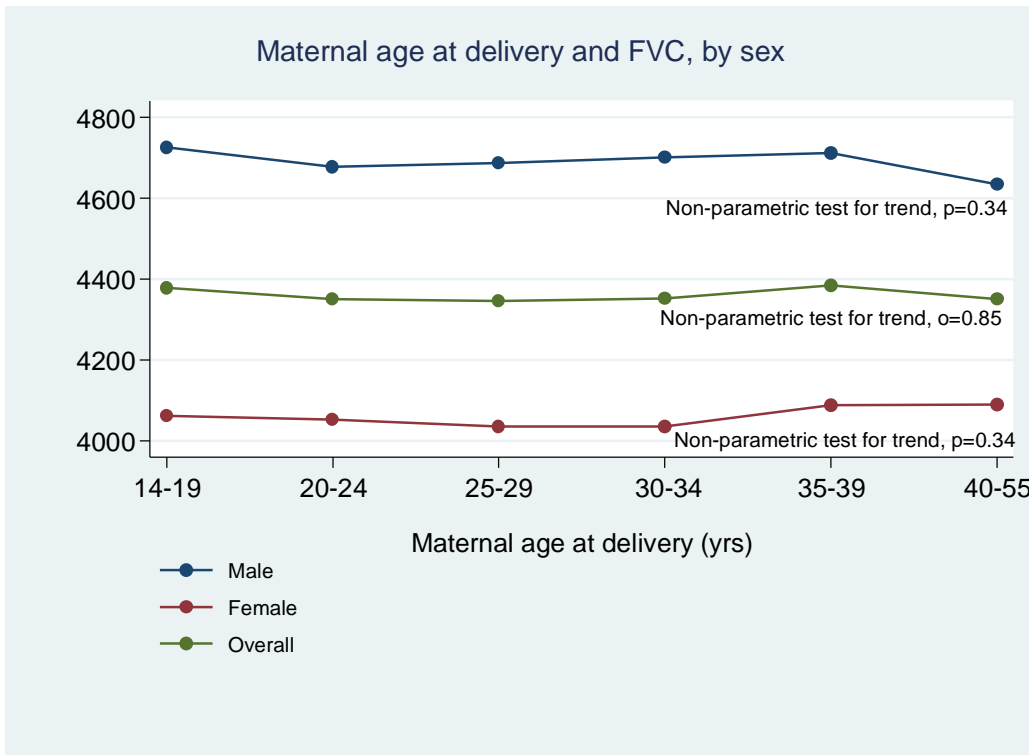
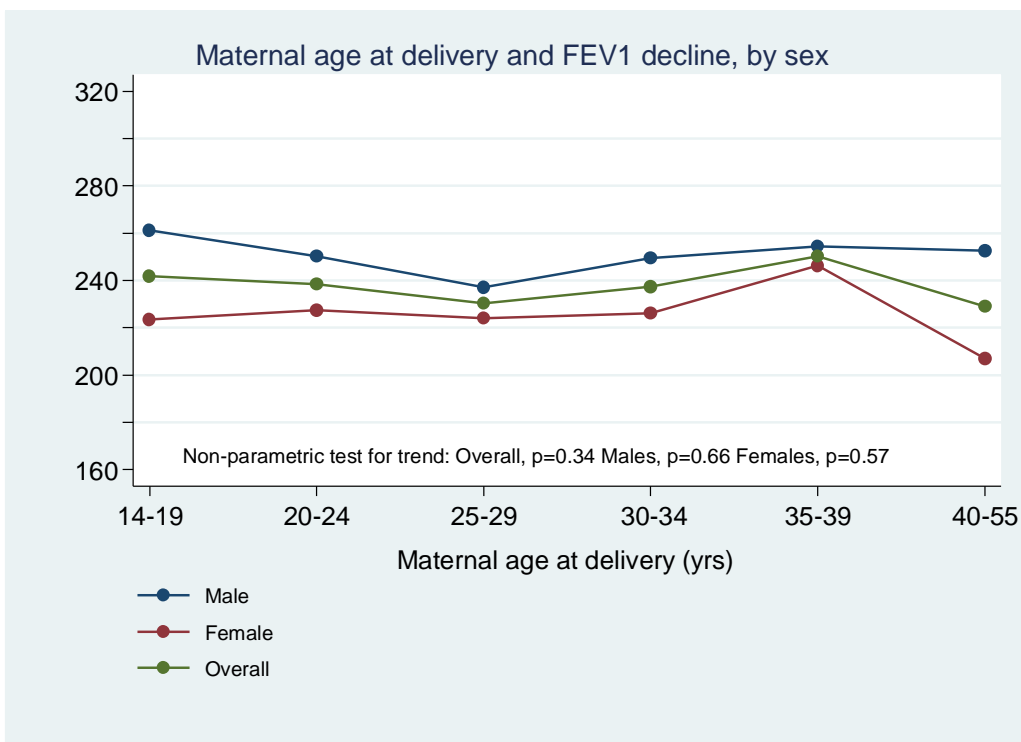


Figure E2. Maternal age at delivery and FEV₁ decline from an adjusted mixed model with country and centres as a random intercepts

(Decline in forced expiratory volume in one second in ml per year of follow-up, FEV₁ in ECRHS I minus FEV₁ in ECRHS II, a positive value represents decline)



REFERENCES

1. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J*. 1994;7(5):954-60.
2. Jarvis D KJ, Burney P, Chinn S, Luczynska C, Anto JM, Cerveri I, de Marco R, Gislason T, Heinrich J, Janson C, Kuenzli N, Leynaert B, Neukirch F, Schouten J, Sunyer J, Svanes C, Vermeire P, Wjst M. . The European Community Respiratory Health Survey II. *Eur Respir J*. 2002;20(5):1071-9.
3. Sunyer J, Pekkanen J, Garcia-Esteban R, Svanes C, Kunzli N, Janson C, et al. Asthma score: predictive ability and risk factors. *Allergy*. 2007;62(2):142-8.
4. Chinn S, Jarvis D, Melotti R, Luczynska C, Ackermann-Liebrich U, Anto JM, et al. Smoking cessation, lung function, and weight gain: a follow-up study. *Lancet*. 2005;365(9471):1629-35; discussion 00-1.
5. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology*. 2011;22(5):745.