ONLINE SUPPLEMENTARY MATERIAL

Title: Parental prepuberty overweight and offspring lung function

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Table S1. Distribution by RHINESSA study centre in the paternal and maternal lines.

		Paternal line		Maternal line	
Country	**Centre**	**N° of offspring**	**N° of fathers**	**N° of offspring**	**N° of mothers**
Denmark	Aarhus	18	17	2	2
Estonia	Tartu	24	21	66	51
Iceland	Reykjavik	41	33	61	50
Norway	Bergen	182	119	168	118
Sweden	Goteborg	20	19	32	30
	Umea	34	27	44	33
	Uppsala	39	32	45	39
Spain	Albacete	9	5	10	8
	Huelva	12	7	32	19
Australia	Melbourne	41	28	50	38
	Total	**420**	**308**	**510**	**388**

Table S2. Natural direct effects* on offspring's pre-bronchodilator FEV_1/FVC (model 2) within the paternal line.

	Offspring's overweight before puberty‡ beta (95%CI)		Offspring's adult height (cm) beta (95%CI)		Offspring's FEV_1/FVC beta (95%CI)	
	Sons	Daughters	Sons	Daughters	Sons	Daughters
Fathers' overweight (*vs* never)						
before puberty	0.55 (-0.19, 1.19)	0.83 (0.32, 1.45)	**-3.41 (-6.18, -0.57)**	-2.11 (-4.59, 0.64)	0.97 (-1.9, 4.14)	-0.84 (-2.94, 1.19)
at age 30 years but not before puberty	0.07 (-4.26, 0.88)	-0.02 (-0.79, 0.57)	-0.28 (-3.56, 6.85)	-0.2 (-2.73, 1.86)	0.24 (-3.97, 3.57)	-0.02 (-2.71, 2.44)
Offspring's overweight before puberty	-	-	0.38 (-1.17, 1.99)	**-1.16 (-2.28, -0.09)**	-0.13 (-1.4, 1.05)	-0.2 (-1.17, 0.79)
Offspring's height in adulthood (cm)	-	-	-	-	-0.12 (-0.23, 0.01)	-0.09 (-0.21, 0.02)

* Difference (beta) in offspring's expected lung function value for the change in exposure status, keeping offspring's height and/or offspring's overweight at their expected value when the exposure is absent. Model 2 also includes the potential confounders and adjusting variables of the mediators (fathers' low education level) and of the outcomes (fathers' low education level and offspring's age and ever smoking). Beta is a probit regression coefficient for the effect on the latent mediator (offspring's overweight before puberty) and a linear regression coefficient for the effect on offspring's adult height and FEV1/FVC.

‡ Offspring's overweight before puberty was considered as a continuous latent mediator variable.

95%CI: 95% confidence interval. The statistically significant effects are indicated in bold.

Table S3. Natural indirect effects* on offspring's pre-bronchodilator FEV_1/ FVC (model 2) within the paternal line.

		Offspring's FEV_1/FVC beta (95%CI)	
	Indirect effects	Sons	Daughters
Father's overweight (*vs* never)			
before puberty	via offspring's overweight	-0.07 (-1.11, 0.68)	-0.17 (-1.18, 0.73)
	via offspring's height	0.4 (-0.05, 0.95)	0.2 (-0.08, 0.68)
	via offspring's overweight and height	-0.02 (-0.21, 0.08)	0.09 (-0.03, 0.33)
at age 30 years but not before puberty	via offspring's overweight	-0.01 (-1.54, 3.16)	0 (-0.37, 0.45)
	via offspring's height	0.03 (-0.77, 0.52)	0.02 (-0.19, 0.35)
	via offspring's overweight and height	0 (-0.13, 0.64)	0 (-0.12, 0.1)

* Difference (beta) in offspring's expected lung function value when the exposure is present, but offspring's height and/or offspring's overweight change from their expected value when the exposure is absent to their expected value when the exposure is present. Model 2 also includes the potential confounders and adjusting variables of the mediators (fathers' low education level) and of the outcomes (fathers' low education level and offspring's age and ever smoking).
95%CI: 95% confidence interval. The statistically significant effects are indicated in bold.

Table S4. Natural direct effects* on offspring's pre-bronchodilator FEV_1/FVC (model 2) within the maternal line.

	Offspring's overweight before puberty‡ beta (95%CI)		Offspring's adult height (cm) beta (95%CI)		Offspring's FEV_1/FVC beta (95%CI)	
	Sons	Daughters	Sons	Daughters	Sons	Daughters
Mothers' overweight (*vs* never)						
before puberty	0.16 (-0.42, 0.67)	0.23 (-0.15, 0.58)	-1.74 (-3.91, 0.44)	-1.73 (-3.55, 0.20)	0.39 (-1.33, 2.09)	1.58 (0.02, 3.15)
at age 30 years but not before puberty	0.13 (-0.45, 0.62)	-0.05 (-0.53, 0.37)	-0.43 (-2.70, 1.79)	-0.67 (-2.74, 1.44)	0.01 (-2.01, 2.02)	0.87 (-0.86, 2.59)
Offspring's overweight before puberty	-	-	0.33 (-0.99, 1.59)	-0.37 (-1.49, 0.73)	-0.12 (-1.16, 0.97)	0.22 (-0.64, 1.12)
Offspring's height in adulthood (cm)	-	-	-	-	**-0.14 (-0.25, -0.02)**	-0.01 (-0.12, 0.10)

* Difference (beta) in offspring's expected lung function value for the change in exposure status, keeping offspring's height and/or offspring's overweight at their expected value when the exposure is absent. Model 2 also includes the potential confounders and adjusting variables of the mediators (mothers' low education level) and of the outcomes (mothers' low education level and offspring's age and ever smoking). Beta is a probit regression coefficient for the effect on the latent mediator (offspring's overweight before puberty) and a linear regression coefficient for the effect on offspring's adult height and FEV_1/FVC.

‡ Offspring's overweight before puberty was considered as a continuous latent mediator variable.

95%CI: 95% confidence interval. The statistically significant effects are indicated in bold.

Table S5. Natural indirect effects* on offspring's pre-bronchodilator FEV_1/ FVC (model 2) within the maternal line.

		Offspring's FEV_1/FVC beta (95%CI)	
	Indirect effects	Sons	Daughters
Mother's overweight (*vs* never)			
before puberty	via offspring's overweight	-0.02 (-0.39, 0.37)	0.05 (-0.21, 0.38)
	via offspring's height	0.24 (-0.06, 0.70)	0.02 (-0.19, 0.26)
	via offspring's overweight and height	-0.01 (-0.08, 0.06)	0.00 (-0.02, 0.03)
at age 30 years but not before puberty	via offspring's overweight	-0.02 (-0.39, 0.31)	-0.01 (-0.31, 0.21)
	via offspring's height	0.06 (-0.28, 0.42)	0.01 (-0.13, 0.15)
	via offspring's overweight and height	-0.01 (-0.09, 0.04)	0.00 (-0.02, 0.02)

* Difference (beta) in offspring's expected lung function value when the exposure is present, but offspring's height and/or offspring's overweight change from their expected value when the exposure is absent to their expected value when the exposure is present. Model 2 also includes the potential confounders and adjusting variables of the mediators (mothers' low education level) and of the outcomes (mothers' low education level and offspring's age and ever smoking).
95%CI: 95% confidence interval. The statistically significant effects are indicated in bold.

Table S6. Natural indirect effects* on offspring's post-bronchodilator FEV_1 and FVC (model 1) or FEV_1/ FVC (model 2) within the paternal line.

		Offspring's FEV_1 (mL) beta (95%CI)		Offspring's FVC (mL) beta (95%CI)		Offspring's FEV_1/FVC beta (95%CI)	
	Indirect effects	Sons	Daughters	Sons	Daughters	Sons	Daughters
Father's overweight (*vs* never)							
before puberty	via offspring's overweight	1 (-77, 86)	17 (-40, 86)	8 (-81, 114)	28 (-37, 111)	-0.04 (-1.19, 0.86)	-0.21 (-1.14, 0.65)
	via offspring's height	**-165 (-312, -29)**	-71 (-163, 21)	**-223 (-410, -41)**	-96 (-221, 27)	0.34 (-0.11, 0.96)	0.23 (-0.07, 0.77)
	via offspring's overweight and height	10 (-37, 89)	-23 (-77, 6)	14 (-49, 120)	-32 (-102, 9)	-0.02 (-0.23, 0.09)	0.08 (-0.03, 0.31)
at age 30 years but not before puberty	via offspring's overweight	0 (-233, 118)	-4 (-48, 29)	1 (-339, 102)	-7 (-58, 33)	-0.01 (-1.87, 2.80)	0.05 (-0.43, 0.62)
	via offspring's height	0 (-153, 317)	15 (-86, 90)	0 (-210, 429)	20 (-118, 117)	0.00 (-0.7, 0.45)	-0.05 (-0.33, 0.36)
	via offspring's overweight and height	1 (-262, 48)	6 (-14, 51)	2 (-358, 65)	8 (-19, 68)	0.00 (-0.11, 0.54)	-0.02 (-0.19, 0.05)

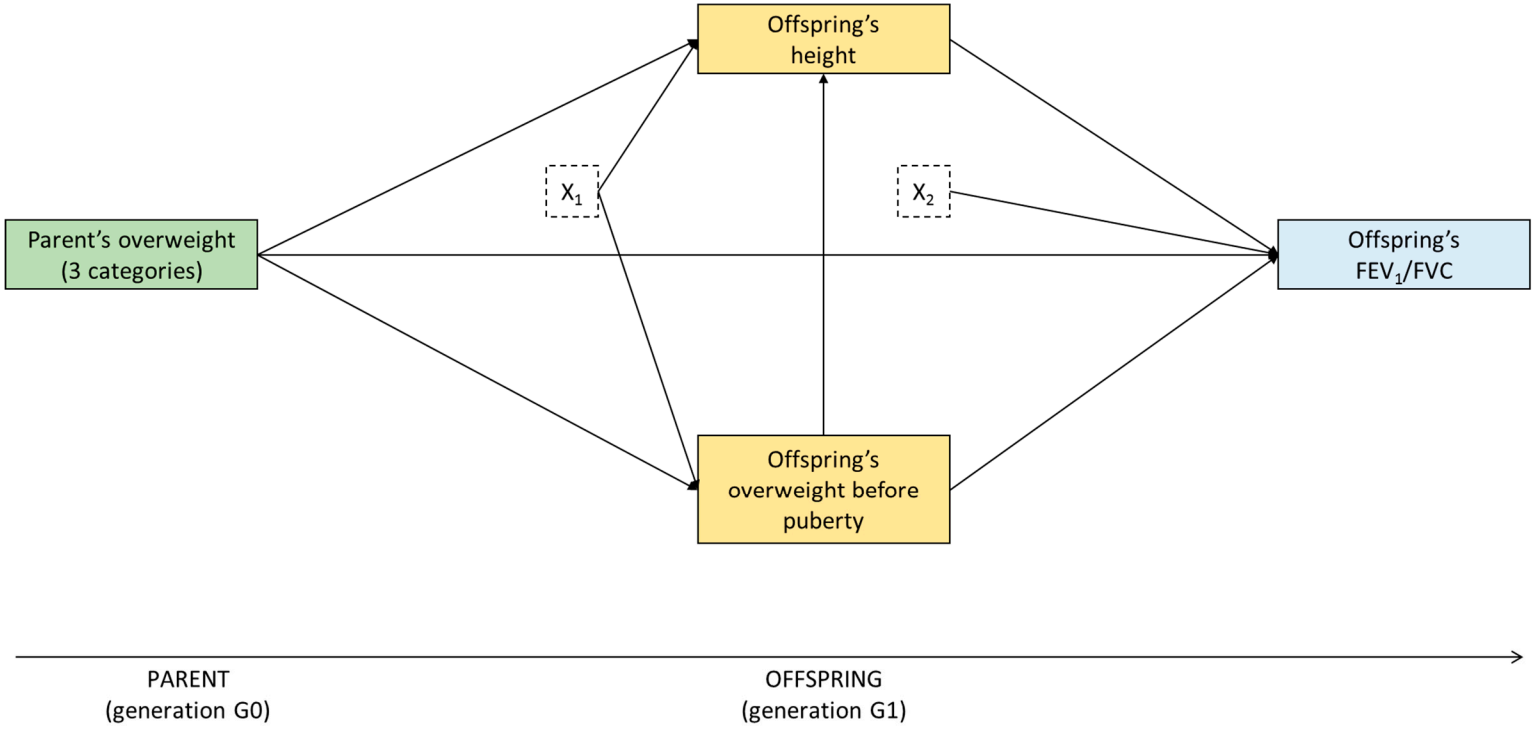
* Difference (beta) in offspring's expected lung function value when the exposure is present, but offspring's height and/or offspring's overweight change from their expected value when the exposure is absent to their expected value when the exposure is present. Model 1 and model 2 also include the potential confounders and adjusting variables of the mediators (fathers' low education level) and of the outcomes (fathers' low education level and offspring's age and ever smoking).
95%CI: 95% confidence interval. The statistically significant effects are indicated in bold.

Table S7. Natural indirect effects* on offspring's post-bronchodilator FEV_1 and FVC (model 1) or FEV_1/ FVC (model 2) within the maternal line.

		Offspring's FEV_1 (mL) beta (95%CI)		Offspring's FVC (mL) beta (95%CI)		Offspring's FEV_1/FVC beta (95%CI)	
	Indirect effects	Sons	Daughters	Sons	Daughters	Sons	Daughters
Mother's overweight (*vs* never)							
before puberty	via offspring's overweight	7 (-35, 55)	7 (-13, 39)	8 (-42, 67)	9 (-15, 48)	-0.01 (-0.41, 0.40)	-0.02 (-0.31, 0.22)
	via offspring's height	-77 (-179, 19)	-67 (-138, 3)	-109 (-256, 26)	-86 (-176, 4)	0.23 (-0.05, 0.70)	0.12 (-0.06, 0.41)
	via offspring's overweight and height	3 (-18, 30)	-4 (-23, 7)	5 (-25, 43)	-5 (-29, 9)	-0.01 (-0.10, 0.06)	0.01 (-0.02, 0.05)
at age 30 years but not before puberty	via offspring's overweight	6 (-38, 51)	-3 (-34, 20)	7 (-44, 60)	-4 (-45, 23)	-0.01 (-0.40, 0.37)	0.01 (-0.20, 0.31)
	via offspring's height	-22 (-129, 79)	-18 (-102, 64)	-31 (-182, 115)	-23 (-128, 81)	0.06 (-0.27, 0.43)	0.03 (-0.14, 0.24)
	via offspring's overweight and height	3 (-14, 33)	2 (-13, 18)	4 (-20, 47)	2 (-17, 23)	-0.01 (-0.10, 0.05)	0.00 (-0.04, 0.03)

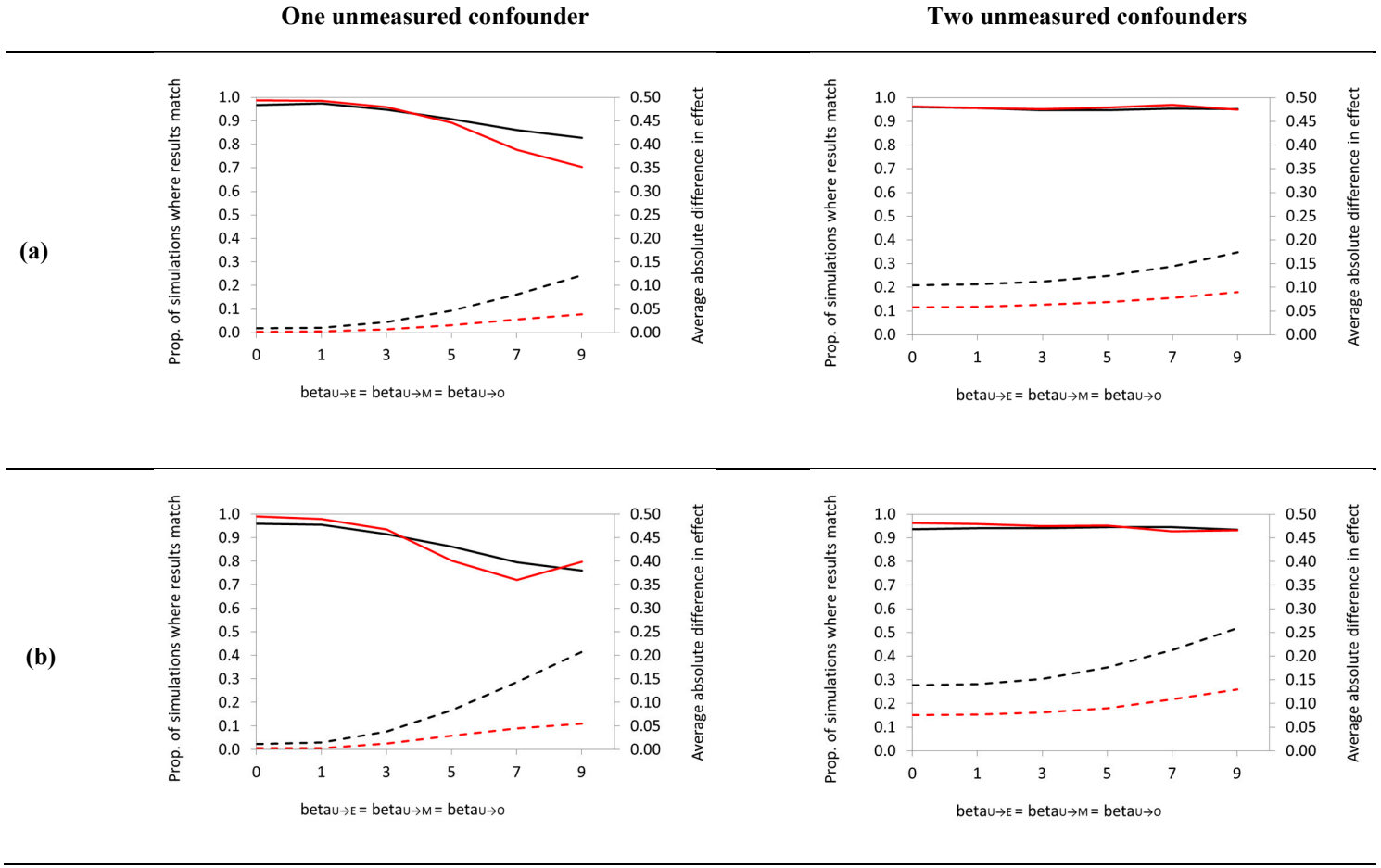
* Difference (beta) in offspring's expected lung function value when the exposure is present, but offspring's height and/or offspring's overweight change from their expected value when the exposure is absent to their expected value when the exposure is present. Model 1 and model 2 also include the potential confounders and adjusting variables of the mediators (mothers' low education level) and of the outcomes (mothers' low education level and offspring's age and ever smoking).
95%CI: 95% confidence interval. The statistically significant effects are indicated in bold.

Figure S1. Graphical representation of the mediation model for FEV_1/FVC in sons or daughters within the paternal or maternal lines. (*Model 2*).



The green box represents the exposure of interest, the yellow boxes the mediators and the blue boxes the outcomes. The dotted boxes represent the set of potential confounders and adjusting variables of the mediators (X_1: parent's low education level) and of the outcomes (X_2: parent's low education level and offspring's age and smoking).

Figure S2. Proportion of Monte Carlo simulations where results match (solid line) and average absolute difference (dashed line) in the average direct (black line) and indirect (red line) effects of fathers' overweight start in prepuberty on sons' lung function (whether one or two unmeasured confounders are included or excluded from the models). Outcomes: (a) FEV_1 and (b) FVC.



SUPPLEMENTARY INFORMATION ON THE EUROPEAN COMMUNITY RESPIRATORY HEALTH SURVEY (ECRHS)

ECRHS III

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