MINIMAL SUFFICIENT ADJUSTMENT SET

We explored whether the potential confounders included in *model 1* and *model 2* represent the "*minimal sufficient adjustment set*" to estimate the total effect of each exposure on the outcomes (i.e. the smallest group of measured covariates that needs to be included in order to eliminate confounding). We used directed acyclic graphs (DAGs) [1] in DAGitty (*dagitty.net*) (**figure S1** and **figure S2**). DAGs help to minimize the magnitude of the bias in the estimates, to avoid the risk of over-adjustment and to establish whether the statistical models used are the most parsimonious.

The DAG analysis supported the assumption that the minimal sufficient adjustment set contains grandparents' education level, fathers' age, education level and occupational class, mother's smoking before or after offspring's birth, and offspring's age, education level, sex and smoking ("*education_GP*", "*age_F*", "*education_F*", "*occupation_F*", "*smoke_M*", "*age_O*", "*education_O*", "*sex_O*" and "*smoke_O*" in **figure S1** and **figure S2**).

UNMEASURED CONFOUNDING

We evaluated the impact of unmeasured confounding [2] on the estimate of the natural direct and indirect effects of fathers' and grandmothers' smoking on offspring's lung function, using the Umediation package (*github.com/SharonLutz/Umediation*) in R3.6.1. Umediation makes it possible to simulate unmeasured confounding of the exposure-outcome, exposure-mediator and mediator-outcome relationships in order to investigate how the results would change if up to two unmeasured confounders were included in the mediation models.

We carried out the simulation analyses as follows:

- In *model 1* and *model 2*, we subdivided the paths in order to simulate unmeasured confounding within a single-exposure, single-mediator, single-outcome framework. Then, we added up to two unmeasured normally distributed confounders with mean 0 and variance 0.001 to the models ("U_1" and "U_2" variables). **Figure S3** shows how the data were simulated for "*smoke_GM*" (exposure), "*FEV1_F*" (mediator) and "*FEV1_O*" (outcome).
- As inputs for the simulations, we used the beta regression coefficients obtained from the cluster-robust (cluster variable: centre) linear models, defined as follows:
  - "*FEV1_O*" as the outcome and "*smoke_GM*", "*education_F*", "*FEV1_F*", "*occupation_F*", "*smoke_F*", "*smoke_M*", "*age_O*", "*education_O*", "*sex_O*", "*smoke_O*" as covariates;
  - "*FVC_O*" as the outcome and "*smoke_GM*", "*education_F*", "*FVC_F*", "*occupation_F*", "*smoke_F*", "*smoke_M*", "*age_O*", "*education_O*", "*sex_O*", "*smoke_O*" as covariates;
  - "*FEV1/FVC_O*" as the outcome and "*smoke_GM*", "*education_F*", "*FEV1/FVC_F*", "*occupation_F*", "*smoke_F*", "*smoke_M*", "*age_O*", "*education_O*", "*sex_O*", "*smoke_O*" as covariates;
  - "*FEV1_F*" as the outcome and "*education_GP*", "*smoke_GM*", "*age_F*", "*education_F*", "*occupation_F*", "*smoke_F*" as covariates;
  - "*FVC_F*" as the outcome and "*education_GP*", "*smoke_GM*", "*age_F*", "*education_F*", "*occupation_F*", "*smoke_F*" as covariates;
  - "*FEV1/FVC_F*" as the outcome and "*education_GP*", "*smoke_GM*", "*age_F*", "*education_F*", "*occupation_F*", "*smoke_F*" as covariates;
  - "*smoke_GM*" as the outcome and no covariates (null model);
  - "*smoke_F*" as the outcome and no covariates (null model).

  The beta regression coefficients were estimated from 800 bootstrap samplings of one offspring per parent (n = n° offspring = n° fathers = 274). This was done to avoid the "$2 \rightarrow 2 \rightarrow 1$" mediation pattern.
- We carried out the simulations under multiple scenarios for the effects (beta regression coefficients) of the unmeasured confounder "U_1" on "*smoke_GM*" and "*smoke_F*" (exposure; $beta_{U \rightarrow E}$), on "*FEV1_F*", "*FVC_F*" and "*FEV1/FVC_F*" (mediator; $beta_{U \rightarrow M}$), and on "*FEV1_O*", "*FVC_O*" and "*FEV1/FVC_O*" (outcome; $beta_{U \rightarrow O}$), by fixing $beta_{U \rightarrow E} = beta_{U \rightarrow M} = beta_{U \rightarrow O}$ = 0, 1, 3, 5, 7 and 9. We repeated the simulations by adding the second unmeasured confounder "U_2" to the models under the same assumptions.
- We selected 1,000 simulation runs and 1,000 Monte Carlo draws for the nonparametric bootstrap in each of the simulation analyses.

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2 Lutz SM, Thwing A, Schmiege S, *et al*. Examining the role of unmeasured confounding in mediation analysis with genetic and genomic applications. BMC Bioinformatics 2017; 18: 344.

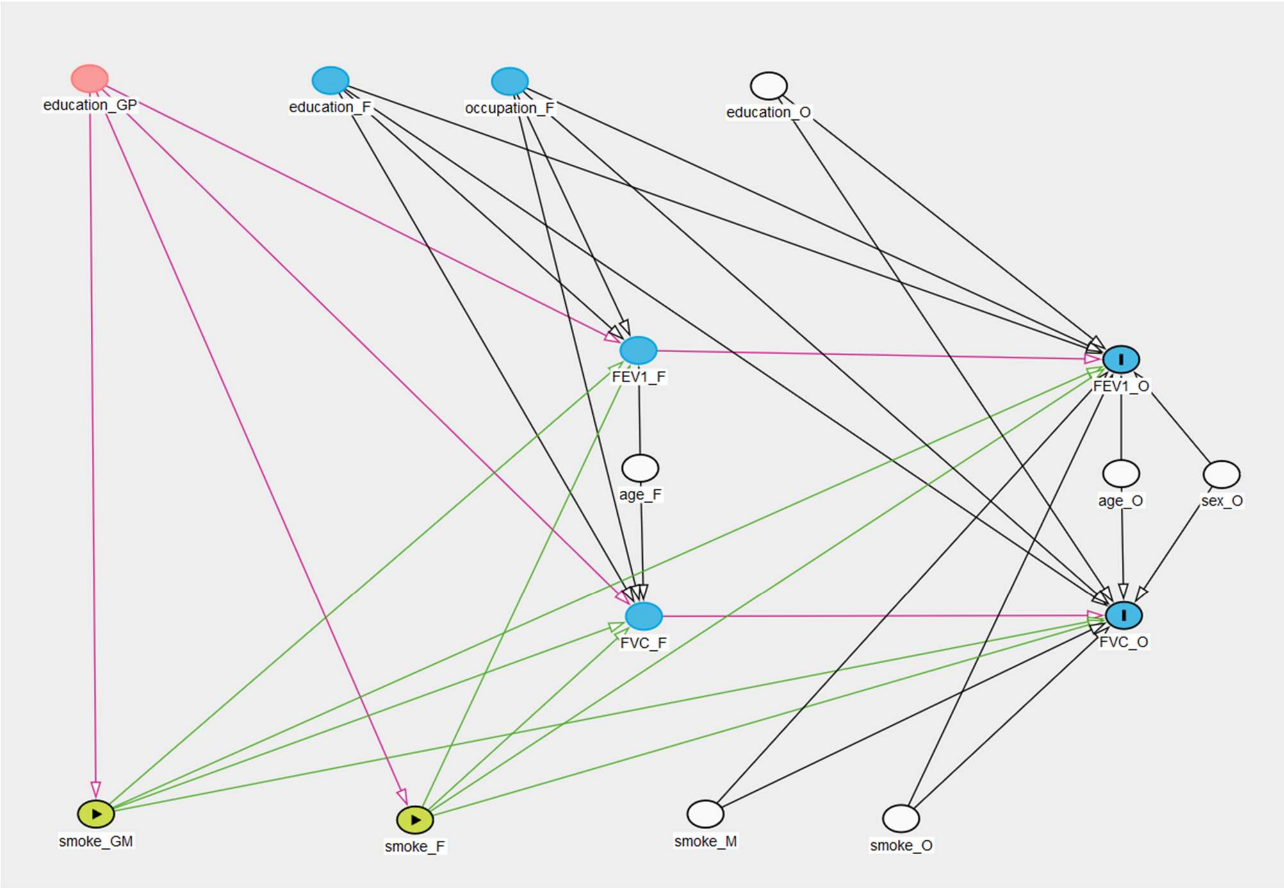

Figure S1. Directed acyclic graph used to check if the potential confounders included in *model 1* represent the "*minimal sufficient adjustment set*". Grandparents (generation G0): "education_GP", grandparents' education level; "smoke_GM", grandmother's smoke. Father/mother (generation G1): "age_F", father's age; "education_F", father's education level; "FEV1_F", father's FEV_1 z-score; "FVC_F", father's FVC z-score; "occupation_F", father's occupational class; "smoke_F", father's smoke; "smoke_M", mother's smoke. Offspring (generation G2): "age_O", offspring's age; "education_O", offspring's education level; "FEV1_O", offspring's FEV_1 z-score; "FVC_O", offspring's FVC z-score; "sex_O", offspring's sex; "smoke_O", offspring's smoke.

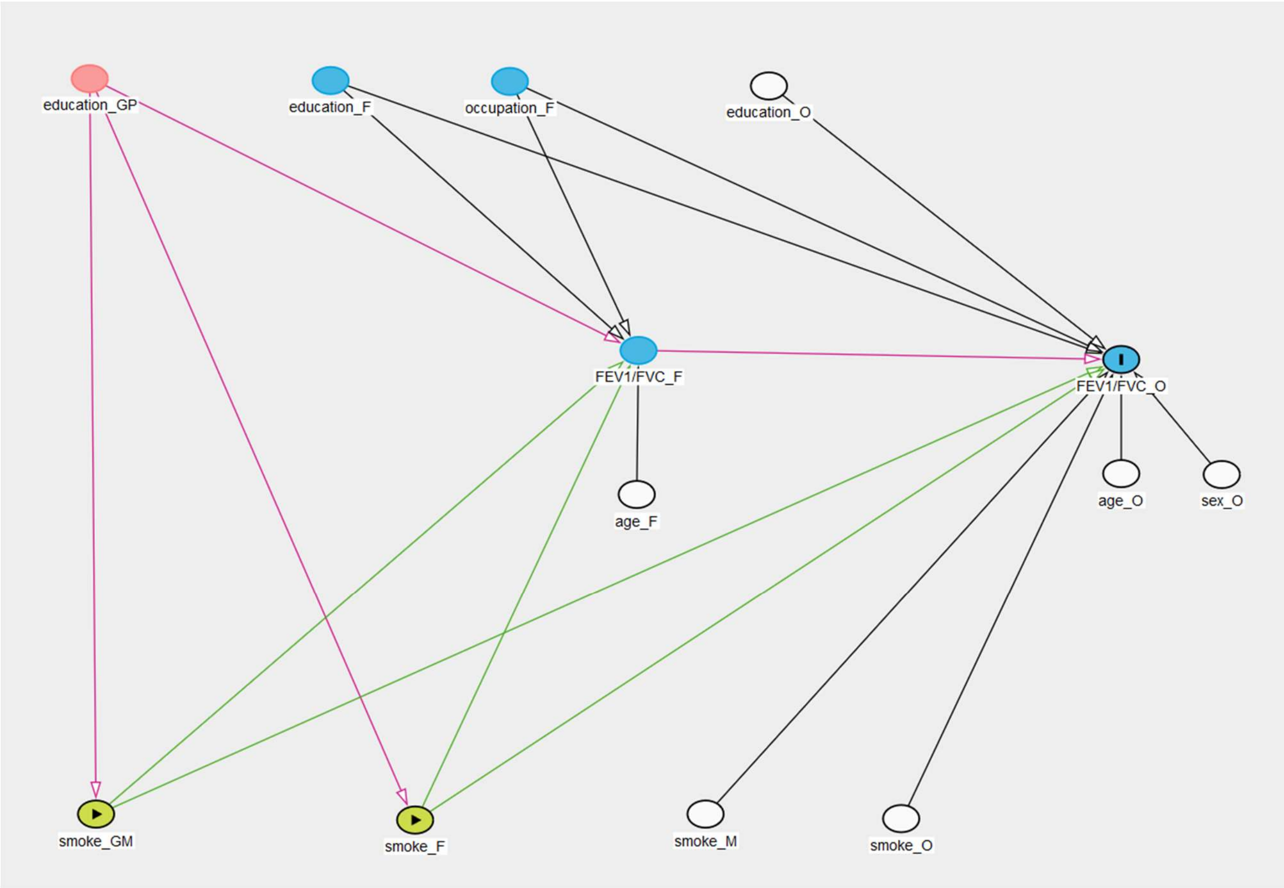

Figure S2. Directed acyclic graph used to check if the potential confounders included in *model 2* represent the "*minimal sufficient adjustment set*". Grandparents (generation G0): "education_GP", grandparents' education level; "smoke_GM", grandmother's smoke. Father/mother (generation G1): "age_F", father's age; "education_F", father's education level; "FEV1/FVC_F", father's FEV_1/FVC z-score; "occupation_F", father's occupational class; "smoke_F", father's smoke; "smoke_M", mother's smoke. Offspring (generation G2): "age_O", offspring's age; "education_O", offspring's education level; "FEV1/FVC_O", offspring's FEV_1/FVC z-score; "sex_O", offspring's sex; "smoke_O", offspring's smoke.

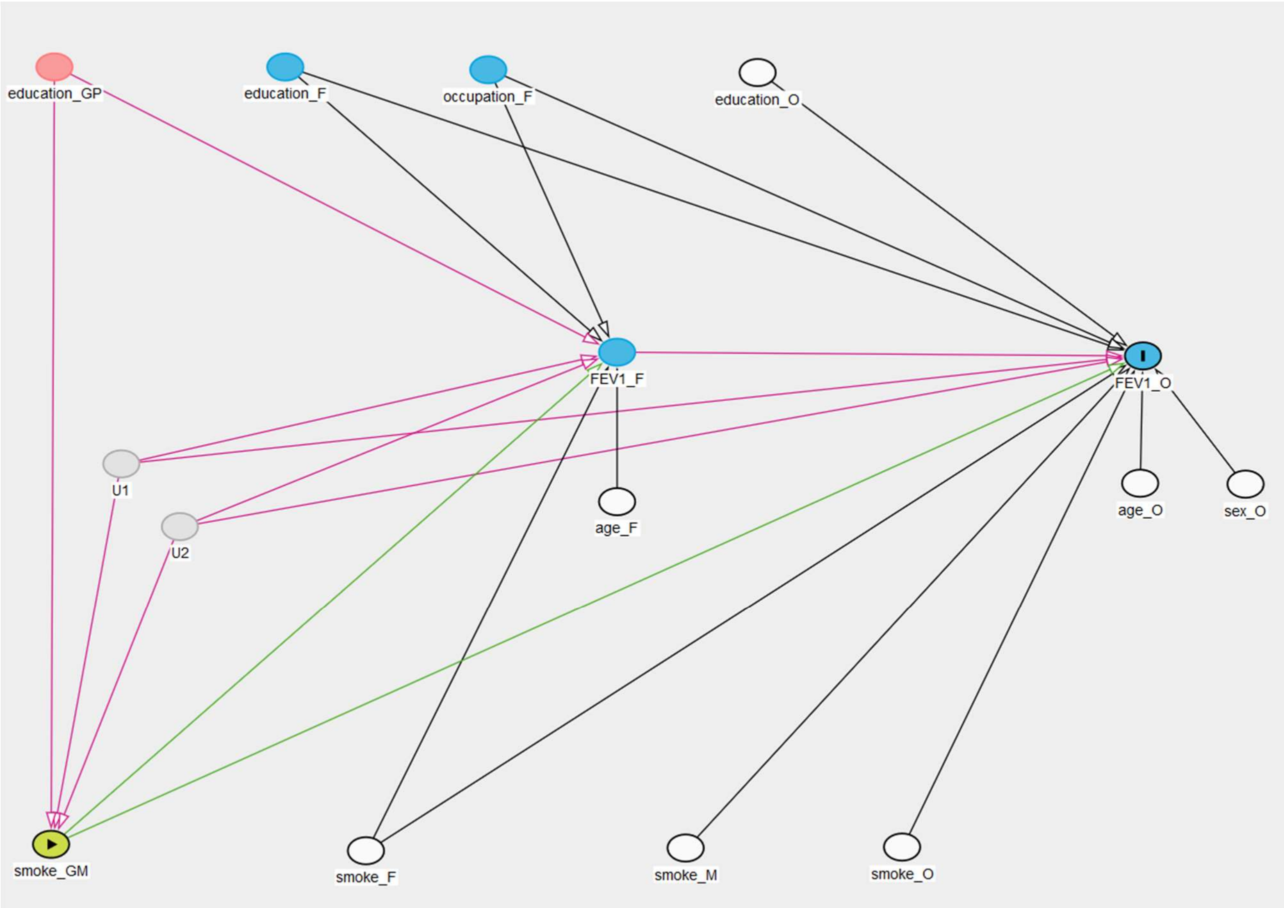

Figure S3. Directed acyclic graph used to simulate the impact of two unmeasured confounders ("U_1" and "U_2") on the direct and indirect effects of grandmothers' smoking in pregnancy on offspring's FEV_1 z-score. Grandparents (generation G0): "education_GP", grandparents' education level; "smoke_GM", grandmother's smoke. Father/mother (generation G1): "age_F", father's age; "education_F", father's education level; "FEV1_F", father's FEV_1 z-score; "occupation_F", father's occupational class; "smoke_F", father's smoke; "smoke_M", mother's smoke. Offspring (generation G2): "age_O", offspring's age; "education_O", offspring's education level; "FEV1_O", offspring's FEV_1 z-score; "sex_O", offspring's sex; "smoke_O", offspring's smoke.

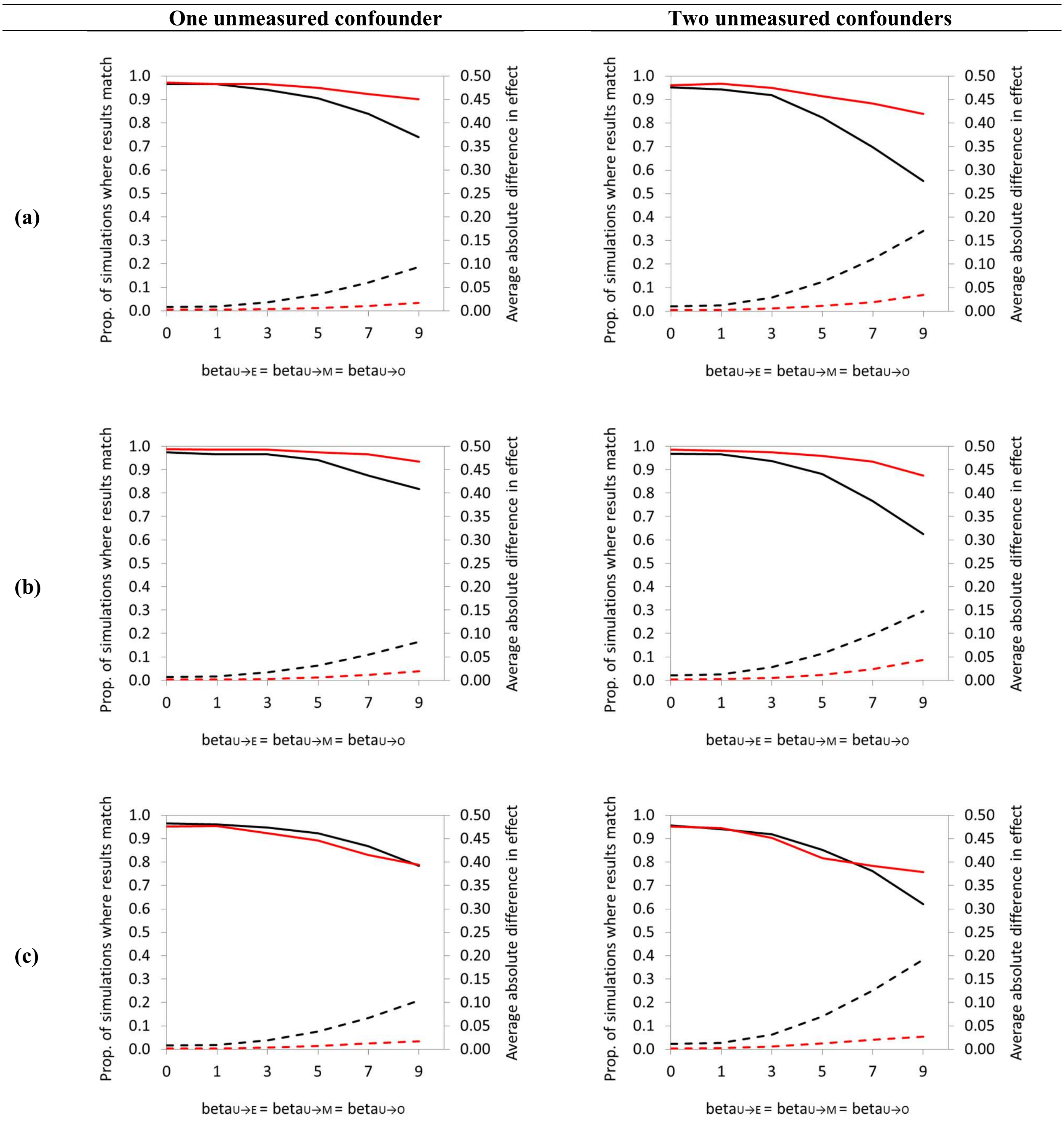

Figure S4. Proportion of Monte Carlo simulations where results match (solid line) and average absolute difference (dashed line) in the average direct (black line) and indirect (red line) effects of fathers' smoking initiation in prepuberty on offspring's lung function (whether one or two unmeasured confounders are included or excluded from the models). Outcomes: (a) FEV_1, (b) FVC and (c) FEV_1/FVC z-scores.

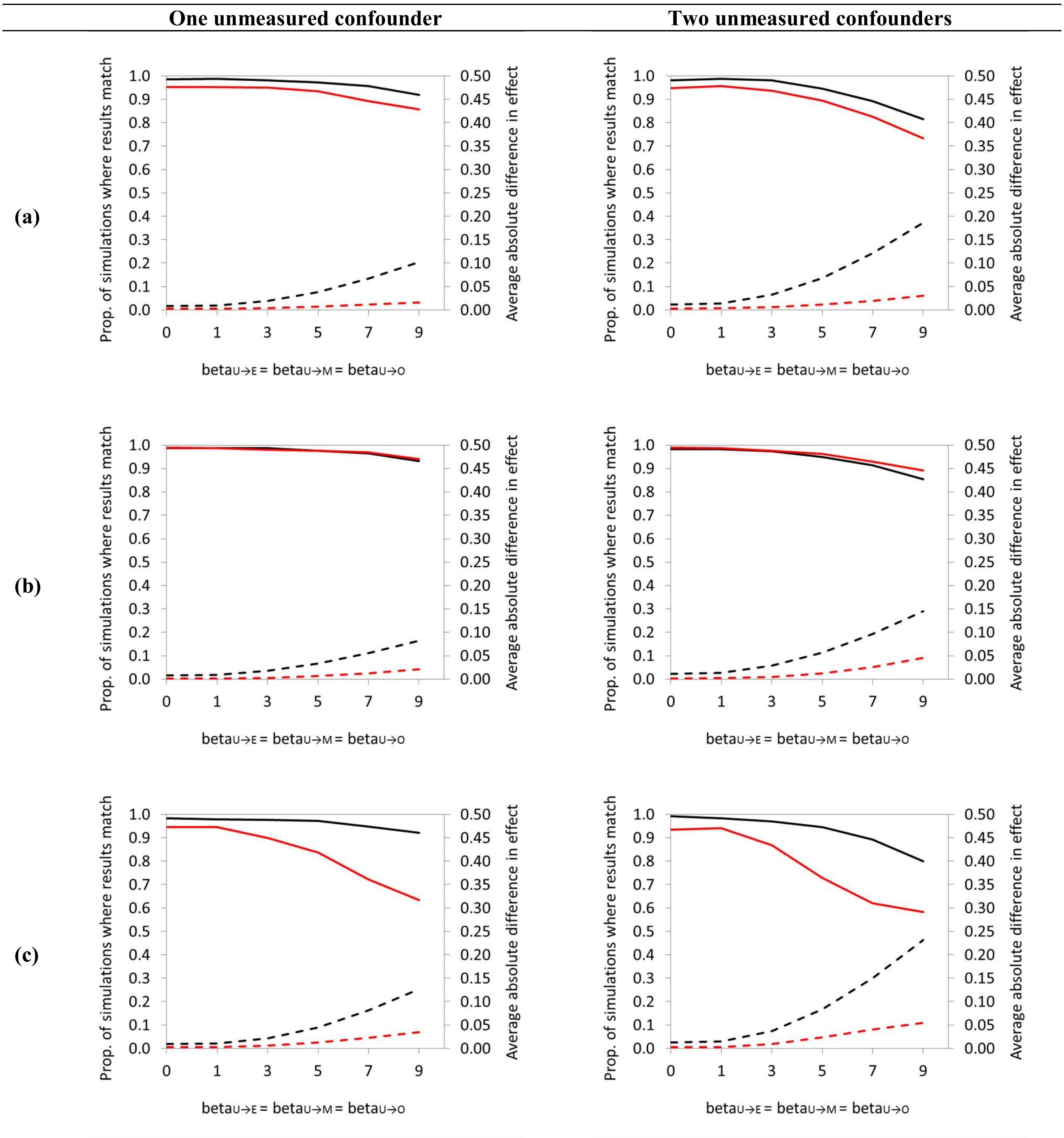

Figure S5. Proportion of Monte Carlo simulations where results match (solid line) and average absolute difference (dashed line) in the average direct (black line) and indirect (red line) effects of grandmothers' smoking in pregnancy on offspring's lung function (whether one or two unmeasured confounders are included or excluded from the models). Outcomes: (a) FEV_1, (b) FVC and (c) FEV_1/FVC z-scores.

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

ECRHS I

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Financial support: The following grants helped to fund the local studies. **Australia**: Asthma Foundation of Victoria, Allen and Hanbury's; **Belgium**: Belgian Science Policy Office, National Fund for Scientific Research; **Estonia:** Estonian Science Foundation, grant no 1088; **France:** Ministère de la Santé, Glaxo France, Institut Pneumologique d'Aquitaine, Contrat de Plan Etat-Région Languedoc-Rousillon, CNMATS, CNMRT (90MR/10, 91AF/6), Ministre Delegué de la Santé, RNSP; **Germany**: GSF, Bundesminister für Forschung und Technologie; **Italy:** Ministero dell'Università e della Ricerca Scientifica e Tecnologica, CNR, Regione Veneto grant RSF n. 381/05.93; **Norway:** Norwegian Research Council project no. 101422/310; **Spain:** Fondo de Investigación Sanitaria (#91/0016-060-05/E, 92/0319 and #93/0393), Hospital General de Albacete, Hospital General Juan Ramón Jiménez, Dirección Regional de Salud Pública (Consejería de Sanidad del Principado de Asturias), CIRIT (1997 SGR 00079) and Servicio Andaluz de Salud; **Sweden:** The Swedish Medical Research Council, the Swedish Heart Lung Foundation, the Swedish Association against Asthma and Allergy; **Switzerland:** Swiss national Science Foundation grant 4026-28099; **UK:** National Asthma Campaign, British Lung Foundation, Department of Health, South Thames Regional Health Authority.

Coordination: The co-ordination of this work was supported by the European Commission; the authors and participants are grateful to the late C. Baya and M. Hallen for their help during the study, and to K. Vuylsteek and the members of the COMAC for their support.

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Financial Support: **Australia:** National Health and Medical Research Council; **Belgium: Antwerp:** Fund for Scientific Research (G.0402.00), University of Antwerp, Flemish Health Ministry; **Estonia: Tartu:** Estonian Science Foundation grant no 4350; **France: (All)** Programme Hospitalier de Recherche Clinique—Direction de la Recherche Clinique (DRC) de Grenoble 2000 number 2610, Ministry of Health, Ministère de l'Emploi et de la Solidarité, Direction Génerale de la Santé, Centre Hospitalier Universitaire (CHU) de Grenoble; **Bordeaux:** Institut Pneumologique d'Aquitaine; **Grenoble:** Comité des Maladies Respiratoires de l'Isere; **Montpellier:** Aventis (France), Direction Regionale des Affaires Sanitaires et Sociales Languedoc-Roussillon; **Paris:** Union Chimique Belge-Pharma (France), Aventis (France), Glaxo France; **Germany: Erfurt:** GSF—National Research Centre for Environment and Health, Deutsche Forschungsgemeinschaft (FR1526/1-1); **Hamburg:** GSF—National Research Centre for Environment and Health, Deutsche Forschungsgemeinschaft (MA 711/4-1); **Iceland: Reykjavik:** Icelandic Research Council, Icelandic University Hospital Fund; **Italy: Pavia:** GlaxoSmithKline Italy, Italian Ministry of University and Scientific and Technological Research (MURST), Local University Funding for Research 1998 and 1999; **Turin:** Azienda Sanitaria Locale 4 Regione Piemonte (Italy), Azienda Ospedaliera Centro Traumatologico Ospedaliero/Centro Traumatologico Ortopedico—Istituto Clinico Ortopedico Regina Maria Adelaide Regione Piemonte; **Verona:** Ministero dell'Università e della Ricerca Scientifica (MURST), Glaxo Wellcome spa; **Norway: Bergen:** Norwegian Research Council, Norwegian Asthma and Allergy Association, Glaxo Wellcome AS, Norway Research Fund; **Spain: Albacete:** Fondo de Investigaciones Sanitarias (97/0035-01, 99/0034-01, and 99/0034-02), Hospital Universitario de Albacete, Consejeria de Sanidad; **Barcelona:** Sociedad Espanola de Neumología y Cirugía Toracica, Public Health Service (R01 HL62633-01), Fondo de Investigaciones Sanitarias (97/0035-01, 99/0034-01, and 99/0034-02), Consell Interdepartamental de Recerca i Innovació Tecnològica (1999SGR 00241), Instituto de Salud Carlos III, Red de Centros de Epidemiología y Salud Pública (C03/09), Red de Bases moleculares y fisiológicas de las Enfermedades Respiratorias (C03/011), Red de Grupos Infancia y Medio Ambiente (G03/176); **Huelva:** Fondo de Investigaciones Sanitarias (97/0035-01, 99/0034-01, and 99/0034-02); **Galdakao:** Basque Health Department; **Oviedo:** Fondo de Investigaciones Sanitarias (97/0035-02, 97/0035, 99/0034-01, 99/0034-02, 99/0034-04, 99/0034-06, 99/350, and 99/0034-07), European Commission (EU-PEAL PL01237), Generalitat de Catalunya (CIRIT 1999 SGR 00214), Hospital Universitario de Albacete, Sociedad Española de Neumología y Cirugía Torácica (SEPAR R01 HL62633-01), Red de Centros de Epidemiología y Salud Pública (C03/09), Red de Bases moleculares y fisiológicas de las Enfermedades Respiratorias (C03/011), Red de Grupos Infancia y Medio Ambiente (G03/176, 97/0035-01, 99/0034-01, and 99/0034-02); **Sweden: Göteborg, Umea, and Uppsala**: Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences and Allergy Research, Swedish Asthma and Allergy Foundation, Swedish Cancer and Allergy Foundation, Swedish Council for Working Life and Social Research (FAS); **Switzerland: Basel:** Swiss National Science Foundation, Swiss Federal Office for Education and Science, Swiss National Accident Insurance Fund; **UK: Ipswich and Norwich**: Asthma UK (formerly known as National Asthma Campaign).

Cordination: The coordination of this work was supported by the European Commission, as part of their Quality of Life programme (QLK4-CT-1999-01237).

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Financial Support: **Australia:** National Health & Medical Research Council; **Belgium: Antwerp South, Antwerp City:** Research Foundation Flanders (FWO) (G.0.410.08.N.10); **Estonia: Tartu:** Estonian Ministry of Education (SF0180060s09); **France:** (**All centres**) Ministère de la Santé, Programme Hospitalier de Recherche Clinique (PHRC) national 2010; **Bordeaux:** INSERM U897 Université Bordeaux segalen; **Grenoble:** Comite Scientifique AGIRadom 2011; **Paris:** Agence Nationale de la Santé, Région Ile de France, domaine d'intérêt majeur (DIM); **Germany: Erfurt:** German Research Foundation (HE 3294/10-1); **Hamburg:** German Research Foundation (MA 711/6-1, NO 262/7-1); **Iceland: Reykjavik:** The Landspitali University Hospital Research Fund, University of Iceland Research Fund, ResMed Foundation, California, USA, Orkuveita Reykjavikur (Geothermal plant), Vegagerðin (The Icelandic Road Administration (ICERA). **Italy: (All centres)** Italian Ministry of Health, Chiesi Farmaceutici SpA; **Verona:** Cariverona foundation, Education Ministry (MIUR). **Norway:** Norwegian Research council (214123), Western Norway Regional Health Authorities (911631), Bergen Medical Research Foundation. **Spain:** Fondo de Investigación Sanitaria (PS09/02457, PS09/00716, 09/01511, PS09/02185, PS09/03190), Servicio Andaluz de Salud, Sociedad Española de Neumología y Cirurgía Torácica (SEPAR 1001/2010), Fondo de Investigación Sanitaria (PS09/02457); **Barcelona:** Fondo de Investigación Sanitaria (FIS PS09/00716); **Galdakao:** Fondo de Investigación Sanitaria (FIS 09/01511); **Huelva:** Fondo de Investigación Sanitaria (FIS PS09/02185), Servicio Andaluz de Salud; **Oviedo:** Fondo de Investigación Sanitaria (FIS PS09/03190). **Sweden: (All centres)** The Swedish Heart and Lung Foundation, The Swedish Asthma and Allergy Association, The Swedish Association against Lung and Heart Disease, Swedish Research Council for health, working life and welfare (FORTE); **Göteborg:** Swedish Council for Working life and Social Research; **Umea:** Vasterbotten Country Council ALF grant. **Switzerland:** The Swiss National Science Foundation (33CSCO-134276/1, 33CSCO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099), The Federal office for forest, environment and landscape, The Federal Office of Public Health, The Federal Office of Roads and Transport, the canton's government of Aargan, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais, and Zürich, the Swiss Lung League, the canton's Lung League of Basel Stadt/Basel, Landschaft, Geneva, Ticino, Valais, and Zurich, SUVA, Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH, Abbott Diagnostics, European Commission (018996) (GABRIEL), Wellcome Trust (WT 084703MA). **UK:** Medical Research Council (92091). Support also provided by the National Institute for Health Research through the Primary Care Research Network.

Coordination: The coordination was funded through the Medical Research Council (92091).

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Ethics approval: Ethics approval was obtained by all centres from the appropriate ethics committees: **Antwerp City and Antwerp South:** Adviescommissie Medische Ethiek UZA-UA (CME); **Tartu:** Research Ethics Committee of the University of Tartu, Estland (N° 209T-17); **French centres:** Comite de protection des personnes, Sud V Est (N° 2011-A00013-38); **German centres:** Ethik-Kommission der Bayerischen Landesarztekammer (N° 10015); **Reykjavik:** National Biotecs Committe of Iceland (NBCI) (N° VSNb2011090016/03.11); **Pavia:** Fondazione IRCCS Policlinico 'San Matteo' (N° P-20110024215); **Turin:** Comitato Etico dell'Azienda Sanitaria Locale TO/2 di Torino (N° 569/09/08); **Verona:** Comitato Etico per la Sperimentazione dell'Azienda Ospedaliera Istituti Ospitalieri di Verona (N° 1393); **Bergen:** Universitetet i Bergen, Regional komité for medisinsk og helsefaglig forskningsetikk, Vest-Norge (REK Vest) (N° 2010/759); **Albacete:** Comité de Ética e Investigación de Complejo Hospitalario de Albacete (N° 04/09); **Barcelona:** Comité Ético de Investigación Clínica del Instituto Municipal de Asistencia Sanitaria, Barcelona, Spain (N° PS09/00716); **Galdakao:** Comité Éticode Investigación del Hospital de Galdakao, Spain (N° 20101104); **Huelva:** Comisión de Investigación del Hospital Juan Ramón Jiménez de Huelva (N° 20090417); **Oviedo:** Comité Ético de Investigación Clínica Regional, Hospital Universitario Central de Asturias (N° 20110415); **Swedish centres:** Ethics Committee at the Medical Faculty, Uppsala University (N° 1999/313 and 2010/068); **Basel:** Swiss Academy of Medical Sciences and the ethics committee of Basel (N° PV123/00,157/00); **UK centres:** NRES Committee London - Stanmore (REC Reference 11/LO/0965 IRAS number 70769).