**SUPPLEMENTARY METHODS**

**Genome-wide association studies of asthma in population-based cohorts confirm known and suggested loci and identify an additional association in the HLA region**

**Stage 1 – Brief study description, funding acknowledgement and phenotype definition**

**FINRISK STUDY**

*Description:* A population survey of risk factors for chronic diseases in Finland. The survey has been executed every five years from 1972 using independent, random and representative population samples from five geographical areas of the country. Participants have filled in a health-related questionnaire and undergone a physical examination including measurement of anthropometric traits and blood draw (E[1](#_ENREF_1)).

*Funding:* Mainly funded by the Finnish National Institute for Health and Welfare with additional financial support from the Academy of Finland (grant number 129494, 139635), the Finnish Foundation for Cardiovascular Research, and the Sigrid Juselius Foundation. Participants were genotyped as part of the COROGENE (Genetic Predisposition of Coronary Heart Disease in Patients Verified with Coronary Angiogram) (E[2](#_ENREF_2)) and MIGen (Myocardial Infarction Genetics Consortium) (E[3](#_ENREF_3)) efforts.

Asthma status: For the FINRISK 1992 cohort, individuals who have answered “YES” to the question “***Have you had any of the following diseases diagnosed or treated by a doctor during the past year (last 12 months)?:*** Asthma of the lungs”. were considered to have asthma. For the FINRISK 1997, 2002 and 2007 cohorts, information about asthma was based on the following question: “***Have you ever been diagnosed with asthma?”* Participants responding “YES” were considered to have asthma.** In all FINRISK surveys the rest of the participants served as controls if their age was less than or equal to 70 years and they did not report pulmonary emphysema, or chronic bronchitis during the last 12 months.

*Smoking status:* Participants were considered as never smokers if they a**nswered “NO” to the question *“Have you ever smoked?”*** and as ex smokers if they had quit smoking at least a month ago. Current smokers were participants who smoked regularly at the time of the survey or had been smoking regularly less than 1 month ago.

*Allergy status:* **Information about allergy was based on the question *“Have you ever had hay fever of other allergic nasal symptoms?”* Participants responding “YES, during the last 12 months”, and those responding “YES, over a year ago” were considered to have allergy.**

***Framingham Heart Study (FHS)***

*Description:*Began in 1948 by recruiting an Original Cohort of 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts, who had not yet developed overt symptoms of cardiovascular disease or suffered a heart attack or stroke (E[4](#_ENREF_4)). Since that time the study has added an Offspring Cohort of 5,124 individuals in 1971 and a Third Generation Cohort of 4,095 individuals in 2002 (E[5](#_ENREF_5), [6](#_ENREF_6)). The Offspring Cohort is made up of the offspring of the members of the Original Cohort and their spouses, and the Third Generation Cohort is made up of the children of the Offspring cohort. Individuals in the FHS had exams every two years consisting of a detailed medical history, physical examination, and laboratory tests. We used data from the exam questions described below for the purposes of determining asthma cases and controls and to determine smoking and allergy statuses.

*Funding:* Supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center.

*Asthma status:* For the Original Cohort, data from Exams 1 and 5 were used. Individuals who answered “yes” to any asthma question were coded as asthma cases (“yes” to “bronchial asthma, alone” or “allergy and asthma, together” at Exam 1 or “asthma, onset before age 16,” “asthma, onset age 16 or after,” or “asthma, age of onset unknown” at Exam 5). Individuals with a response of “yes” to the question “lifetime history of chronic pulmonary disease” at Exam 2 were excluded from both cases and controls. All remaining individuals were coded as asthma controls. For the Offspring Cohort, data from Exams 2 and 7 were used. Individuals who answered “yes” to any asthma question were coded as asthma cases (“yes” to “asthma” at Exam 2 or “yes, new” or “yes, old” to “have you had asthma in the interim?” at Exam 7). Individuals with a response of “yes” to “chronic obstructive lung disease” or “chronic bronchitis” at Exam 2 were excluded from both cases and controls. Individuals with a response of “yes, now” or “yes, not now” to “non-cardiovascular medications: bronchodilators and aerosols” were excluded from the controls. All remaining individuals were coded as asthma controls. For the Third Generation Cohort, individuals who answered “yes” to “asthma: was it diagnosed by a doctor or other health professional?” were coded as asthma cases. Individuals who answered “no” to both “asthma: was it diagnosed by a doctor or other health professional?” and “have you ever had asthma?” were coded as asthma controls. Individuals who answered “yes” to any of the following questions were excluded from both the cases and controls: “have you ever had COPD?,” “have you ever had pulmonary fibrosis?,” “have you ever had chronic bronchitis?,” “have you ever had emphysema?.”

*Smoking status:* For the Original Cohort, data from Exam 5 were used. Current smokers answered “smokes now” to the question “history of smoking, present habit.” Former smokers answered “does not smoke now, but smoked formerly,” and never smokers answered “never smoked.” For the Offspring Cohort, data from Exams 1, 2, and 7 were used. Current smokers answered “yes” to “smoked cigarettes regularly in last year” (Exam 7) or “smoking now” (Exam 2). Former smokers answered “no” to “smoked cigarettes regularly in last year” (Exam 7) and “yes” to “ever smoked regularly” (Exam 2) or “smoked at least 1 year” (Exam 1). Never smokers answered “no” to “ever smoked” or “ever smoked regularly” (Exam 2). For the Third Generation Cohort, current smokers answered “yes” to “if ever smoked cigarettes regularly: do you now smoke?.” Former smokers answered “yes” to “have you ever smoked cigarettes regularly?” and “no” to “if ever smoked cigarettes regularly: do you now smoke?.” Never smokers answered “no” to “have you ever smoked cigarettes regularly?.”

*Allergy status:* For the Original Cohort, data from Exam 1 were used. Individuals who answered “allergy, alone” or “allergy and asthma, together” to “history of allergy or asthma” were classified as allergy cases. For the Offspring Cohort, no allergy data were available. For the Third Generation Cohort, individuals who answered “yes” to “have you ever had hay fever (allergy involving the nose and/or eyes)?” were classified as allergy cases.

**Health 2000 Study**

*Description:* The study was conducted in 2000 (E[7](#_ENREF_7)) and included home interview, several questionnaires, laboratory and anthropometrical measurements, spirometry with bronchodilator test and clinical examination of a physician. The data were completed by record linkage with the National Hospital Discharge Register and the National Social Insurance Institutions register data on reimbursement of asthma medication.

*Funding:* The study was mainly funded by the Finnish National Institute for Health and Welfare. H2000 participants were genotyped as part of the HDL extremes study (E[8](#_ENREF_8)) and the Sanger Institute/Wellcome Trust efforts for GENMETS (Genetic Background and Molecular Pathogenesis of Metabolic Syndrome and Its component Risk Factor Traits).

*Asthma status:* **Information about asthma was based on the following question: *“Has a doctor ever diagnosed you with one of the following illnesses?”* One of the listed illnesses was asthma and those who responded “YES” were considered to have asthma. The rest of the participants were taken as controls if their age was less than or equal to 70 years and they never had had chronic bronchitis.**

*Smoking status:*Information about smoking was taken from a question with five alternatives: (1) I smoke daily; (2) I smoke occasionally; (3) I have quit smoking 1-12 months ago; (4) I have quit smoking more than a year ago; (5) I have never smoked. Participants choosing alternatives 1 or 2 were considered as current smokers; those choosing 3 or 4 were considered as ex-smokers; and those choosing 5 were considered as never smokers.

*Allergy status:* **Information about allergy was based on responses under the subheading: *“Other diseases diagnosed by a doctor”.* One of the alternatives gives was *“allergy, rhinitis; for example hay fever or other allergic rhinitis”* Those responding “YES” to this item were considered as having allergy.**

**Helsinki Birth Cohort Study (HBCS)**

*Description:*The study includes 8760 subjects born in Helsinki between 1934 and 1944. Between 2001 and 2004, a representative subset of 928 males and 1075 females participated in a clinical study focusing upon cardiovascular and metabolic outcomes and cognitive functions (E[9](#_ENREF_9)). Information on asthma, smoking and alcohol intake is available from questionnaires for 2003 individuals who participated in the clinical study. Information on hospitalization due to alcohol abuse is available from the National Hospital Discharge Register. Psychological questionnaires have been used to assess personality characteristics including data on impulsivity. GWAS has been done on these individuals participating in the clinical study (n~2000) at the mean age of ~62 years.

*Funding:* Financial support was received from the Academy of Finland, Samfundet Folkhälsan, Finnish Diabetes Research Foundation, Finska Läkaresällskapet, Finnish Foundation for Cardiovascular Research; Yrjö Jahnsson Foundation, Foundation Liv och Hälsa and Academy of Finland (grants number 129287 and134839).

*Asthma status:* Information about asthma was based on the following question: *“Have you ever had any of the following illnesses diagnosed or treated by a doctor?”* One of the listed illnesses was *“Asthma of the lungs”* and those responding “YES” to this item were considered as having asthma. Those participants who responded to the same question as having emphysema or chronic bronchitis were excluded and the others were taken as controls. All participants were less than 70 years of age.

*Smoking status:* Information about smoking was taken from a question with three alternatives: (1) I smoke daily; (2) I smoke occasionally; (3) I have never smoked. Participants choosing alternatives 1 were considered as current smokers; those choosing 2 were considered as ex-smokers; and those choosing 3 were considered as never smokers.

*Allergy status:* Information about allergy was based on the following question: *“Do you have following allergic symptoms? Nasal allergy, hay fever, stuffy nose”* Participants responding “YES” were considered as having allergy.

**Northern Finland Birth Cohort of 1966 (NFBC1966)**

*Description:* This is a prospective follow-up study of 12,058 live births from the two northernmost provinces of Finland, Oulu and Lapland, and cover 96% of the children born in that region between January 1 and December 31, 1966. In 1997, at age 30 years, 8463 survivors still living in Northern Finland or in the capital area received a postal questionnaire and invitation to clinical examinations including DNA sample (71% participated) (E[10](#_ENREF_10), [11](#_ENREF_11)). Please see <http://kelo.oulu.fi/NFBC/> for more details about the study. Informed consent for the use of the data including DNA was obtained from all subjects. The study was approved by the ethics committees in Oulu (Finland) and Oxford (UK) universities in accordance with the Declaration of Helsinki.

*Funding:* Financial support from the Academy of Finland (project grants 104781, 1114194, 120315 and Center of Excellence in Complex Disease Genetics), Oulu University Hospital, Biocenter Oulu, University of Oulu, Finland, the European Commission (EURO-BLCS, Framework 5 award QLG1-CT-2000-01643), NHLBI grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01), ENGAGE project and grant agreement HEALTH-F4-2007-201413, and the Medical Research Council (studentship grant G0500539). We thank Professor Paula Rantakallio (launch of NFBC1966 and 1986), Ms Outi Tornwall and Ms Minttu Jussila (DNA biobanking). DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Institute for Health and Welfare, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki.

*Asthma status:* We defined asthmatic cases as those who answered yes to BOTH conditions which are parts of Question 31 of the main questionnaire administered in 1997 when participants were aged 31 years: 1) “*have you ever asthma during the last 12 months or more than a year ago?”* and 2) “*has this been verified or treated by doctor?”* The remaining individuals served as healthy controls if they did not have any of the following conditions: self-reported asthma but not verified or treated by doctor diagnosis (n=196); individuals with FEV1 less than 70% of predicted for sex and height (n=19); individuals who reported they ever had emphysema, chronic bronchitis, pulmonary bronchial (n=211) or doctor-diagnosed chronic cough (n=402).

*Smoking status:* First we defined the never/ever smoking status by Question 79 *“Have you ever smoked in your life?”* of 31-year questionnaire. Among the Ever smokers, we distinguish the Current Smokers if they answered said that they smoke on at least one day per week to Question 82 *“Do you smoke nowadays?”*. We excluded 43 ever smokers whom we could not distinguish if they were current or ex-smokers.

*Allergy status:* We defined an individual as allergic if they answered yes for either having hay fever or allergic rhinitis during the last 12 months or more than a year ago in Question 31 of main questionnaire.

**Young Finns Study (YFS)**

*Description:* This is a longitudinal population study sample on the evolution of cardiovascular risk factors from childhood to adulthood (E[12](#_ENREF_12)). The first cross-sectional survey was conducted in 1980 in five Finnish university cities and included 3,596 participants who were in the age groups of 3, 6, 9, 12, 15, and 18 years and were randomly chosen from the national population register; equal ratios of males and females were selected in each age group. In 2007, 2204 subjects now aged 30 to 45 years participated in the latest follow-up study.

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*Asthma status:* Information about asthma was based on a following question: *“Do you have at the moment or have you had a long-term illness, handicap or injury diagnosed by a doctor?”* Those responding “YES” and specifying among the given alternatives “Asthma of the lungs”were considered as having asthma. The rest of the participants were taken as controls, except those who reported having chronic bronchitis. All YFS participants were less than 70 years of age.

*Smoking status:* Information about smoking was based on a question with 5 response alternatives as follows: (1) I smoke once a day or more often than once a day; (2) I smoke once a week or more often than once a week but not daily; (3) I smoke less often than once a week; (4) I have stopped smoking; (5) I have never smoked. Participants choosing any of the alternatives 1-3 were taken as current smokers; those choosing the alternative 4 were taken as ex-smokers and those choosing the alternative 5 were taken as never smokers.

 *Allergy status:* Information about allergy was based on the same question as above, i.e., *“Do you have at the moment or have you had a long-term illness, handicap or injury diagnosed by a doctor?”*Those responding “YES”and specifying among the given alternatives *“Allergic rhinitis, for example hay fever”*were taken as having allergy.

**Stage 2 – Brief study description, funding acknowledgement and phenotype definition**

**1958 British Birth Cohort (B58C)**

*Description:* This is a nationwide British birth cohort including participants born in a particular week of 1958. Details of the B58C biomedical follow-up at age 44.5 have been previously reported and a full technical report is available online (<http://www.b58cgene.sgul.ac.uk/report.php>).

*Funding:* The phenotype and genotype data are from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z (E[13](#_ENREF_13)). The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium (E[14](#_ENREF_14)), a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust and the National Institute for Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895). Genotyping for the B58C-GABRIEL and for ECRHS was supported by a contract from the European Commission as part of GABRIEL (A multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community) contract number 018996 under the Integrated Program LSH-2004-1.2.5-1 Post genomic approaches to understand the molecular basis of asthma aiming at a preventive or therapeutic control and grants from the French Ministry of Research (E[15](#_ENREF_15)).

*Asthma status:* Asthma is defined as self-reported ever at either age 33 or age 42 via administered interviews. Healthy controls exclude any history of asthma, wheezing or wheezing bronchitis as reported in the interviews at age 7, 11, 16 and 23, plus exclusions for bronchitis at age 42 and FEV1 less than 70% predicted for sex and height at age 42.

**Australian asthma genetics consortium (AAGC)**

We carried out a GWAS in 2,110 physician-diagnosed asthmatics and 3,857 controls of European ancestry from Australia. Participants were drawn from two cohorts that are described in detail elsewhere (Ferreira et al., in press): the Australian Asthma Genetics Consortium (AAGC) cohort (n=1,810) and the Queensland Institute of Medical Research (QIMR) GWAS cohort (n=4,157). Amongst the 2,110 asthmatic cases, 759 (36%) were diagnosed through clinical examination and 1,351 (64%) reported a lifetime doctor diagnosis of asthma in epidemiological questionnaires. With respect to disease onset, 1,269 (60%) subjects were classified has having childhood asthma (defined by an age-of-onset at or before age 16), 515 (24%) subjects with later onset asthma (age-of-onset after the age of 16) and 326 (16%) with unknown age-of-onset. Fifty-eight percent of asthmatics were atopic, as defined by a positive skin prick test (SPT) response to at least one common allergen; 68% had at least one first-degree relative with asthma; and 36% reported lifetime smoking.

The 3,857 controls included 2,030 (52.6%) individuals who were classified as asthma-free based on clinical examination (3.0%) or epidemiological questionnaires (49.6%). The remaining 1,827 (47.4%) individuals provided no information about their asthma status and were included in the analysis as controls to improve power. SPT information and lifetime smoking status was unavailable for most controls. Overall, the mean age of participants was 34 years (sd=16.2, range 2 to 92) and 45.2% were males. This dataset does not include 1,230 samples from the Busselton cohort analysed in the GABRIEL study.

***Australian Asthma Genetics Consortium collaborators:*** Svetlana Baltic1, Mark Jenkins2, Dale R. Nyholt3, Catherine Hayden4, Patrick Danoy5, Faang Cheah1, John L. Hopper2, Stephen R. Leeder6, Haydn Walters7, Graham Jones8, Désirée Mészáros9, Mary Roberts10, Melissa C. Southey11, Euan R. Tovey12, Loren Price1, Margaret J. Wright3, Scott D. Gordon3, Li P. Chung1, Anjali K. Henders3, Graham Giles13, Paul S. Thomas14, Suzanna Temple1, John B. Whitfield3, Ian Feather15, Stephen Morrison16, Chalermchai Mitrpant1, Warwick J. Britton17, David John2, Andrew S. Kemp18

1 Lung Institute of WA and Centre for Asthma, Allergy and Respiratory Research, University of WA, Perth, Australia.

2 Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, University of Melbourne, Melbourne, Australia.

3 The Queensland Institute of Medical Research, Brisbane, Australia.

4 School of Paediatrics and Child Health, Princess Margaret Hospital for Children, Perth, Australia.

5 University of Queensland Diamantina Institute, Princess Alexandra Hospital, Brisbane, Australia.

6 Australian Health Policy Institute, University of Sydney, Sydney, Australia

7 Menzies Research Institute, Hobart, Australia.

8 University of Western Sydney, Penrith, Australia

9 Menzies Research Institute, Hobart, Australia.

10 Department of Respiratory Medicine, Royal Children's Hospital, Parkville, Australia.

11 Department of Pathology, The University of Melbourne, Melbourne, Australia.

12 Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia.

13 Cancer Epidemiology Centre, The Cancer Council Victoria, Melbourne, Australia.

14 Faculty of Medicine, University of New South Wales, Sydney, Australia.

15 Gold Coast Hospital, Southport, Australia.

16 University of Queensland, Brisbane, Australia.
17 Centenary Institute and University of Sydney, Camperdown, Australia.

18 The Children's Hospital, Westmead, Sydney, Australia.

**European Community Respiratory Health Survey (ECRHS)**

*Description:* This is a multicentre, mainly European, population based survey carried out in 1990s (E[16](#_ENREF_16)) with a follow-up starting in 1998 (E[17](#_ENREF_17)). Questionnaire information is based on information collected through interviewer administered questionnaire (forms available at <http://www.ecrhs.org/>). Participants were aged 20 – 48 (mean of 34) at the first survey and 28 – 56 (mean age 43) at the second survey. Samples were genotyped as part of the GABRIEL consortium (E[15](#_ENREF_15)) and were collected at the follow-up and were mainly European participants and included an enrichment of asthma cases.

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*Asthma status:* We define asthmatic cases if they responded positively to BOTH of the following questions: 1) ever had asthma at first survey (Question 13) or second survey (Question 14) and 2) if it was verified by doctor diagnosis in second survey (Question 14 part 1). The remaining individuals served as healthy controls if they did not have any of the following conditions: self-reported asthma without doctor diagnosis (n=36); reported ever having wheeze in second survey (n=285); FEV1 less than 70% predicted for age, sex and height (n=10).

**European Prospective Investigation of Cancer, Norfolk (EPIC-Norfolk)**

*Description:* EPIC-Norfolk is part of the large multi-centre Europe-wide EPIC programme looking at the connection between diet and cancer (E[18](#_ENREF_18)). There are over 30,000 participants aged 45 – 70 at recruitment who lived in Norwich and the surrounding towns and rural areas. They have been contributing information about their diet, lifestyle and health through questionnaires, and through health checks carried out by EPIC nurses. In 2006, a GWAS for obesity was carried out on 3,867 individuals (E[19](#_ENREF_19)). A case-cohort design was used in which the subcohort (*N=*2,566) was a random sample of the cohort at baseline and cases were part of the remaining individuals with a value of BMI being 30 kg/m2 or greater (N*=*1,301). Unlike controls in the commonly used case-control design, the subcohort was an unselected population sample allowing for a variety of traits to be investigated.

*Funding:* Supported by research programme grant funding from the Cancer Research Campaign and the Medical Research Council, with additional support from Stroke Association, British Heart Foundation, Department of Health, Europe Against Cancer Programme Commission of the European Union, the Food Standards Agency and the Wellcome Trust.

*Asthma status:* Asthmatics were defined as a positive response to the question *"Has the doctor ever told you that you have asthma?"* which was asked at baseline survey. The remaining individuals served as healthy controls unless they had bronchitis or FEV1 < 70% predicted for age, height and sex.

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