

## **Appendices**

### **1. Cohort descriptions**

[1.1. Population descriptions for GWAS discovery cohorts in the Alcohol Genome-wide Association \(AlcGen\) consortium](#)

[1.2. Population descriptions for GWAS discovery cohorts in the Heart and Aging Research in Genomic Epidemiology Plus \(CHARGE+\) Consortium](#)

[1.3. Population descriptions for replication cohorts](#)

### **2. Funding and acknowledgements**

## **1. Cohort descriptions**

### **1.1 Population descriptions for GWAS discovery cohorts in the Alcohol Genome-wide Association (AlcGen) consortium**

#### **Cohorte Lausannoise study (CoLaus)**

The cohort is a random population sample of the city of Lausanne aged 35-75 years. Recruitment began in June 2003 and ended in May 2006. The CoLaus study was approved by the Institutional Ethics Committee of the University of Lausanne and informed consent was appropriately obtained by all participants. All participants attended the outpatient clinic of the University Hospital of Lausanne in the morning after an overnight fast. Data were collected by trained field interviewers in a single visit lasting about 60 min. Alcohol consumption was assessed by questionnaire and measured in units per week. In total 3,121 individuals were included in the analysis.

#### **The Estonian Biobank Cohort (EGCUT)**

The Estonian Biobank Cohort is a population-based cohort of 52000 Estonian residents (81% ethnic Estonians), recruited on volunteer-basis in 2002-2010 ([www.biobank.ee](http://www.biobank.ee)), managed by the Estonian Genome Center, University of Tartu.

#### **The European Prospective Investigation of Cancer - Norfolk study (EPIC-Norfolk)**

The EPIC-Norfolk sample includes 2,566 participants randomly selected from the EPIC-Norfolk Study, a population-based cohort study of 25,663 men and women of European descent aged 39-79 years recruited in Norfolk, UK between 1993 and 1997.

#### **The Erasmus Rucphen Family study (ERF)**

The ERF (1) is a family based study that includes over 3,000 participants descending from 22 couples living in the Rucphen region in the 19th century. All living descendants of these couples and their spouses were invited to take part in the study. The medical ethics committee of Erasmus MC constituted according to the WMO (National Act Medical-scientific research in human beings) approved the Study (MEC 213.575/2002/114). The genotyping for the ERF study was supported by EUROSPAN (European Special Populations Research Network) through the European Commission FP6 STRP grant (018947; LSHG-CT-2006-01947). The ERF study was further supported by grants from the Netherlands Organisation for Scientific Research (NWO), Erasmus MC, the Centre for Medical Systems Biology (CMSB1 and CMSB2) and the Netherlands Genomics Initiative (NGI) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the program "Quality of Life and Management of the Living Resources" of 5th Framework Programme (no. QLG2-CT-2002-01254). High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organisation for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). Exome sequencing analysis in ERF was supported by the ZonMw grant (project 91111025).

#### **The Fenland study (Fenland)**

The Fenland study is a population-based cohort study that uses objective measures

of disease exposure, such as accurate methods of body composition and energy expenditure, to study the interactions between genetic and lifestyle factors that cause obesity and diabetes. The volunteers are recruited from general practice lists in and around Cambridgeshire (Cambridge, Ely, and Wisbech) in the United Kingdom from birth cohorts from 1950–1975.

### **The Younger Finnish Twin Cohort (FinnTwin12)**

The FinnTwin12 cohort is composed of twins born in Finland during 1983-87. The study has a two-stage sampling design. The larger, first-stage study is an epidemiological investigation of five consecutive and complete birth cohorts of Finnish twin children, including questionnaire assessments of both twins and parents at baseline, starting with a family questionnaire (returned by 2724 families, 87% participation rate) that was mailed late in the year before the twins reach age 12, with follow-up of all twins at age 14, 17.5 years and ~22. Nested within this epidemiological, population-based study, is the second-stage of FinnTwin12, an intensive assessment of a sub-sample of twin families. Most of the sub-sample was selected at random, but this random sample (~72%) was then enriched with twins at elevated familial risk for alcoholism. Genome-wide genotyping was performed on the subjects of the intensive sub-sample.

### **The Older Finnish Twin Cohort (FinnTwinOld)**

This sample originates from the Older Finnish Twin Cohort. The 1975, 1981 and 1990 questionnaires for the same-sex twins and the 1996-97 questionnaires for opposite-sex twins requested identical information on the frequency and quantity of alcohol used during an average week (or month), the frequency of passouts experienced during the preceding year, and required a yes/no response to a question on drinking density. Frequency of alcohol use, measured as days' use per month on 5-point scales ("never" to "over 16 days a month") was assessed separately for beer, wine, and spirits. Similarly, quantity was measured on three 7-point scales, with the upper limits defined as consuming >48 bottles of beer (or 10 bottles of wine) per week, or >20 bottles of spirits per month. Wine use did contribute to the consumption measure. For each type of beverage, consumption was converted into grams of absolute alcohol and summed to yield an estimate of total consumption in grams per month using the class midpoints of the categories and the average alcohol content of each beverage type. The script for computing alcohol amount is available from Jaakko Kaprio on request.

### **The Helsinki Birth Cohort Study (HBCS)**

The Helsinki Birth Cohort Study (HBCS) is composed of 8,760 individuals born between the years 1934-44 in one of the two main maternity hospitals in Helsinki, Finland. Between 2001 and 2003, a randomly selected sample of 928 males and 1075 females participated in a clinical follow-up study with a focus on cardiovascular, metabolic and reproductive health, cognitive function and depressive symptoms.

### **The population-based Cooperative Health Research in the Region of Augsburg F3 Study (KORA F3)**

The population-based Cooperative Health Research in the Region of Augsburg (KORA) F3 Study was carried out in 2004-2005 as a follow-up of the MONICA/KORA S3 baseline study (1994-1995). In S3, 4,856 participants were recruited out of a randomized two-stage cluster sample of 6,640 subjects, with equal-sized sex- and

age-strata, from the target population of all German residents in the region of Augsburg aged 25–74 years. The F3 Study included 3,007 participants aged 35–84 years. 1,644 randomly drawn participants aged 35–79 with Affymetrix genotype data and data on alcohol intake were included in the investigations reported.

#### **The population-based Cooperative Health Research in the Region of Augsburg F4 Study (KORA F4)**

The population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 Study was carried out in 2006–2008 as a follow-up of the KORA S4 baseline study (1999–2001). In S4, 4,261 participants were recruited out of a randomized two-stage cluster sample of 6,640 subjects, with equal-sized sex- and age-strata, from the target population of all German residents in the region of Augsburg aged 25–74 years. The F4 Study included 3,080 participants aged 32–81 years. 1814 randomly drawn participants aged 32–81 with Affymetrix genotype data and data on alcohol intake were included in the investigations reported.

#### **LifeLines Cohort Study & Biobank (Lifelines)**

LifeLines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

#### **The London Life Sciences Prospective Population Study (LOLIPOP)**

LOLIPOP is a population based prospective study of 17,606 Indian Asian and 7,766 European men and women aged 35–75 years, recruited from the lists of 58 General Practitioners in West London, United Kingdom between 2003 and 2008 (2, 3). Europeans were of self-reported white ancestry. Assessments of participants were carried out by trained research nurses with an interviewer-administered questionnaire. Anthropometric measurements and blood samples were taken on site. Alcohol consumption was measured in units per week. One unit is equivalent to: a small glass of wine, a single pub measure of spirits, or half a pint of beer/lager. Aliquots of whole blood were stored at -80C and DNA was extracted and genotyping was carried out thereafter. The LOLIPOP study is approved by the local Research Ethics Committees (3). All participants provided written consent for the study.

#### **The Netherlands Study of Depression and Anxiety (NESDA)**

The Netherlands Study of Depression and Anxiety (NESDA) (4), an ongoing cohort study into the long-term course and consequences of depressive and anxiety disorders. Briefly, in 2004–2007 participants aged 18 to 65 years were recruited from the community (19%), general practice (54%) and secondary mental health care (27%), reflecting therefore various settings and developmental stages of psychopathology in order to obtain a full and generalizable picture of the course of psychiatric disorders. A total of 2,981 participants were included, consisting of persons with a current or past depressive and/or anxiety disorder and healthy controls. The research protocol was approved by the ethical committee of participating universities, and all respondents provided written informed consent.

### **The Northern Finland Birth Cohort 1966 (NFBC1966)**

The North Finland Birth Cohort of 1966 (NFBC1966, n=12,058 live born) was designed to study factors affecting preterm birth, low birth weight, and subsequent morbidity and mortality (<http://kelo.oulu.fi/NFBC/>). The longitudinal data collection includes clinical examination and blood sampling at age 31 years, from which data in the current study are drawn. The attendees in the follow-up (71% response rate) were adequately representative of the original cohort as is the final study sample in the present analyses. A total of 4,763 genotyped samples were available from the NFBC1966.

### **Netherlands Twin Register cohort (NTR)**

Netherlands Twin Register (NTR) (5, 6) participants are ascertained based of the presence of twins or triplets in the family and consist of multiples, their parents, siblings and spouses. Twins are born in all strata of society and NTR represents a general sample from the Dutch population.

### **The Australian twin-family study of alcohol use disorder (OZALC)**

This twin/family cohort was based on two groups of twins, born before 1964 and born 1964-71, enrolled in a voluntary Australia-wide twin registry. Twins, their spouses, and first-degree relatives were recruited for a study on alcohol dependence and related phenotypes (7). Alcohol intake in the week preceding blood collection was self-reported, and history of alcohol use and dependence was obtained through structured telephone interviews.

### **The Prevention of RENal and Vascular ENd-stage Disease study (PREVEND)**

The PREVEND study is an ongoing prospective study investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Inhabitants 28 to 75 years of age (n=85,421) in the city of Groningen, The Netherlands, were asked to complete a short questionnaire, 47% responded, and individuals were then selected with a urinary albumin concentration of at least 10 mg/L (n = 7,768) and a randomly selected control group with a urinary albumin concentration less than 10 mg/L (n = 3,395).

### **The Study of Health in Pomerania (SHIP)**

The Study of Health in Pomerania (SHIP) is a population-based project in West Pomerania, the north-east area of Germany (8, 9). A sample from the population aged 20 to 79 years was drawn from population registries. First, the three cities of the region (with 17,076 to 65,977 inhabitants) and the 12 towns (with 1,516 to 3,044 inhabitants) were selected, and then 17 out of 97 smaller towns (with less than 1,500 inhabitants), were drawn at random. Second, from each of the selected communities, subjects were drawn at random, proportional to the population size of each community and stratified by age and gender. Only individuals with German citizenship and main residency in the study area were included. Finally, 7,008 subjects were sampled, with 292 persons of each gender in each of the twelve five-year age strata. In order to minimize drop-outs by migration or death, subjects were selected in two waves. The net sample (without migrated or deceased persons) comprised 6,267 eligible subjects. Selected persons received a maximum of three written invitations. In case of non-response, letters were followed by a phone call or by home visits if contact by phone was not possible. The SHIP population finally comprised 4,308 participants (corresponding to a final response of 68.8%). Alcohol

intake was assessed by questionnaire, including drink-specific quantity-frequency over 30 days (10).

### **TwinsUK**

TwinsUK is based on a sample of 5,654 individuals from the UK. Among these, 3,471 have been genotyped and have data on alcohol intake assessed by self-reported questionnaire, and 1,204 represent one co-twin per family which have been genotyped and have data on alcohol intake assessed by self-reported questionnaire.

### **The Cardiovascular Risk in Young Finns Study (YFS)**

The YFS is a population-based follow up-study started in 1980. The main aim of the YFS is to determine the contribution made by childhood lifestyle, biological and psychological measures to the risk of cardiovascular diseases in adulthood. In 1980, over 3,500 children and adolescents all around Finland participated in the baseline study. The follow-up studies have been conducted mainly with 3-year intervals. The 27-year follow-up study was conducted in 2007 (ages 30–45 years) with 2,204 participants. The study was approved by the local ethics committees (University Hospitals of Helsinki, Turku, Tampere, Kuopio and Oulu) and was conducted following the guidelines of the Declaration of Helsinki. All participants gave their written informed consent.

## **1.2 Population descriptions for GWAS discovery cohorts in the Heart and Aging Research in Genomic Epidemiology Plus (CHARGE+) Consortium**

### **Age, Gene/Environment Susceptibility–Reykjavik (AGES-Reykjavik)**

The AGES-Reykjavik Study (11) is a single center prospective cohort study based on the Reykjavik Study. The Reykjavik Study was initiated in 1967 by the Icelandic Heart Association to study cardiovascular disease and risk factors. The cohort included men and women born between 1907 and 1935 who lived in Reykjavik at the 1967 baseline examination. Re-examination of surviving members of the cohort was initiated in 2002 as part of the AGES-Reykjavik Study.

### **The Atherosclerosis Risk in Communities Study (ARIC)**

The ARIC study (12) consists of a prospective cohort designed to identify the causes and outcomes of cardiovascular disease in 15,792 individuals from 4 communities (Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD). ARIC study participants underwent interviews, fasting venipuncture, and measurement of anthropometrics at the baseline and follow-up examinations. Trained interviewers ascertained basic demographic data, medical history, and information about personal diet habits. A full description of study design is available on the ARIC website (<http://www2.csc.unc.edu/aric/>). In total, 4,106 individuals had both genotyping and alcohol phenotype. Alcohol consumption was ascertained by means of an interviewer-administered dietary questionnaire. Frequency of alcohol consumption was determined as usual weekly intake, with the amount of alcohol consumed in grams per week calculated assuming different serving sizes and alcohol content for beer, wine, and hard liquor. Serving sizes and alcohol content were defined as follows: 'one beer' (12 oz. bottles or cans of beer, 13.2 g), 'one glass of wine' (4 oz. glass, 10.8 g), or 'one shot of liquor or one mixed drink' (1.5 oz. shot

of hard liquor, 15.1 g). The total amount of absolute alcohol ingested weekly for past alcohol consumption was determined by multiplying the number of servings by the amount of alcohol in one serving of the type of alcohol ordinarily drunk. If more than one type was ordinarily drunk, the calculation was made assuming an equal number of drinks of each type. The total amount of absolute alcohol ingested weekly for present alcohol consumption resulted from the addition of absolute alcohol consumed for wine, beer, and hard liquor. The total amount of absolute alcohol drunk during the 24 hours prior to the clinic interview was determined by multiplying the number of drinks by the amount of absolute alcohol in the type of drink consumed. For a drinker who reported less than one drink per week, the alcohol consumption was recorded as zero grams per week. All questions were closed-ended and designed for direct data entry by a trained interviewer. In order to ensure standardization, exact wording and order of questions were followed. Questions were skipped only if specified in the questionnaire instructions.

### **The Cardiovascular Health Study (CHS)**

The CHS is a population-based cohort study of risk factors for coronary heart disease and stroke in adults  $\geq 65$  years conducted across four field centers (13). The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888. The CHS GWAS, which had the primary aim of studying incident cardiovascular events, focused on 3,980 participants who were free of clinical cardiovascular disease at study baseline, consented to genetic testing, and had DNA available for genotyping. A total of 1,908 persons were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke, or transient ischemic attack. Because the other cohorts were predominantly of European descent, the African American participants were excluded from this analysis. In total, 3009 participants with both genotype and alcohol phenotype were included in the analyses.

At the baseline visit and annually, participants separately reported their usual frequency of consumption of beer, wine, and liquor, and the usual number of 12-ounce cans or bottles of beer, 6-ounce glasses of wine, and shots of liquor that they drank on each occasion. The full text of the CHS nutritional questionnaire is publicly available (<http://www.chs-nhlbi.org/forms/r25p3.htm>). At baseline, participants also reported whether they changed their pattern of consumption during the past 5 years and whether they ever regularly consumed 5 or more drinks daily.

### **The Framingham Heart Study (FHS)**

The FHS sample includes the Framingham Heart Study Offspring (14) and the third generation (15) cohorts. In 1971, children and spouses of children of the original FHS cohort participants were recruited into the Framingham offspring cohort, which consists of 5,124 men and women. The FHS offspring participants have been examined every four to eight years unless specified otherwise, common clinical phenotypes from all examinations were available for this investigation. From 2002 to 2005, a third generation cohort of 4,095 individuals was recruited to the FHS. The third generation cohort ( $n=4,095$ ) includes children and spouses of children of the Offspring cohort. In total, 8,955 individuals had both genotyping and alcohol phenotype.

Alcohol consumption was assessed via questionnaire at the study examination closest to the time point of DNA collection.

### **The Health, Aging, and Body Composition (HABC)**

The Health ABC study (16) is a prospective cohort study investigating the associations between body composition, weight-related health conditions, and incident functional limitation in older adults. Health ABC enrolled well-functioning, community-dwelling black (n=1281) and white (n=1794) men and women aged 70-79 years between April 1997 and June 1998. Participants were recruited from a random sample of white and all black Medicare eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas. Participants have undergone annual exams and semi-annual phone interviews. The current study sample consists of 1559 white participants who attended the second exam in 1998-1999 with available genotyping data.

Alcohol consumption at baseline was assessed by asking the participant how many alcoholic drinks he/she consumed in a typical week, during the past 12 months. Furthermore, it was asked whether a person ever drank more than what he/she typically drank in the past 12 months.

### **The Multi-Ethnic Study of Atherosclerosis (MESA)**

The MESA is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease (17). MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants are White, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California, Los Angeles. The current analysis was limited to n=1596 White participants with data available on alcohol consumption through the Food-frequency questionnaire. Data on alcoholic beverage consumption (drinks/day) were obtained on 2,382 Caucasian individuals with genotypes available through MESA SHARe. As a part of a 120-item food frequency questionnaire, participants were asked the frequency they consumed each beer, wine, and liquor or mixed drinks (9 frequency options ranging from rarely/never to six or more drinks/day) (18, 19). Responses to these three line items were summed to estimate total alcoholic drinks consumed each day.

### **The Rotterdam Study (RS)**

The RS (20) is a prospective, population-based study from the well-defined district of Ommoord within the city of Rotterdam, designed to investigate the occurrence and determinants of diseases in the elderly. The cohort was initially defined in 1990 among 7 983 persons who underwent a home interview and extensive physical examination at baseline and during follow-up examinations occurring every 3-4 years (RS-I). The cohort was further extended in 2000 (RS-II) and 2005 (RS-III), establishing a total of 14926 participants.

### **The Women's Genome Health Study (WGHS)**



The WGHS (21) is a prospective cohort of initially healthy, female North American health care professionals at least 45 years old at baseline in 1992-1994, representing participants in the Women's Health Study (WHS) who provided a blood sample at baseline and consent for blood-based analyses. These WHS was 2x2 randomized, placebo controlled trial of aspirin and vitamin E in prevention of cardiovascular disease and cancer over 10 years. Since the end of the trial, follow-up in the WHS/WGHS has continued in observational mode.

### **1.3 Population descriptions for replication cohorts**

#### **Airwave Health Monitoring Study (Airwave)**

The Airwave Health Monitoring Study (22) was established to evaluate possible health risks associated with use of TETRA, a digital communication system used by police forces and other emergency services in Great Britain since 2001. The study has been broadened to investigate more generally the health of the work force. From 2004, participants from each force who agreed to participate were enrolled either with an enrolment questionnaire or a comprehensive health screening performed locally. This includes questionnaire, 7-day food diaries, anthropometry, measurements of cardiovascular and cognitive function, blood chemistry, coagulation and hematology. By March 2015, the study had recruited 53,606 participants, of whom 45,433 had attended the health screening. 12,930 participants with genotype data were included in this analysis.

#### **The Austrian Stroke Prevention Study (ASPS)**

The ASPS study is a single center prospective follow-up study on the effects of vascular risk factors on brain structure and function in the normal elderly population of the city of Graz, Austria. The procedure of recruitment and diagnostic work-up of study participants has been described previously (23, 24). A total of 2,007 participants were randomly selected from the official community register stratified by gender and 5 year age groups. Individuals were excluded from the study if they had a history of neuropsychiatric disease, including previous stroke, transient ischemic attacks, and dementia, or an abnormal neurologic examination determined on the basis of a structured clinical interview and a physical and neurologic examination. During 2 study periods between September 1991 and March 1994 and between January 1999 and December 2003 an extended diagnostic work-up including neuropsychological testing was done in 1,076 individuals aged 45 to 85 years randomly selected from the entire cohort: 509 from the first period and 567 from the second. In 1992, blood was drawn from all study participants for DNA extraction. They were all European Caucasians. Genotyping was performed in 996 participants, and those 829 who passed genotyping quality control and have data on alcohol intake were available for these analyses.

#### **The British 1958 birth cohort (B58C)**

The British 1958 birth cohort (25) is a follow-up study of persons born throughout England, Scotland and Wales one week in March 1958. Alcohol consumption was self-reported at a biomedical examination at age 44-45 years, at which blood sampling was performed with consent for DNA extraction and creation of immortalized cell lines. Genotyping of three non-overlapping subsets of the cohort

was performed by the Wellcome Trust Case-Control Consortium, the Type 1 Diabetes Genetics Consortium and the GABRIEL Asthma Genetics Consortium. The three subsets were combined for imputation using the 1000-genomes phase 1 reference panel, and for subsequent statistical analysis.

### **Data from an Epidemiological Study on the Insulin Resistance syndrome (DESIR)**

General population from ten French Social Security Health Examination Centers.

### **The Finnish Twin Cohort replication sample (FinnTwin replication)**

Sample used for replication consists of subjects from the Older Finnish Twin Cohort and the Younger Finnish Twin Cohorts (non-overlapping with the discovery sample). Please see cohort descriptions of the discovery sample.

### **Genetic Regulation of Arterial Pressure of Humans in the Community Study (GRAPHIC)**

The GRAPHIC Study comprises 2024 individuals from 520 nuclear families recruited from the general population in Leicestershire, UK between 2003-2005 for the purpose of investigating the genetic determinants of blood pressure and related cardiovascular traits. Families were included if both parents aged 40-60 years and two offspring  $\geq 18$  years wished to participate. A detailed medical and lifestyle history including alcohol intake was obtained from study subjects by standardized questionnaires and clinical examination was performed by research nurses following standard procedures.

### **Generation Scotland: Scottish Family Health Study (GS:SFHS)**

GS:SFHS (26) consists of 23,960 individuals recruited at random from general medical practices across Scotland, 21,516 of these attended the research clinic. Eligibility criteria specified that participants were over 18 years of age and had one first-degree relative also willing to participate. Genome-wide SNP data were ascertained for 10,000 individuals, and after quality control, genotype data were available for 9,863 participants, which are the participants used in this study. 7,281 of these individuals self-reported as currently consuming alcohol. Alcohol consumption was assessed using a pre-clinical questionnaire. Participants were identified as current drinkers, former drinkers or never drinkers. Consumption was measured in self-reported units of alcohol consumed in the previous week. The cohort has been described in further detail elsewhere (26).

### **The INGI - Carlantino study (INGI\_CARL)**

This cohort comprises the samples coming from a small village from the southern region of Italy Puglia. For all samples a wide range of information are available including alcohol intake and anthropometric measurements. Moreover for all samples a DNA sample was acquired and was used for genotyping with high density SNP arrays.

### **The INGI - Friuli Venezia Giulia study (INGI\_FVG)**

This cohort comprises the samples coming from a 6 small villages from the northern region of Italy Friuli Venezia Giulia. For all samples a wide range of information are available including alcohol intake and anthropometric measurements. Moreover for all samples a DNA sample was acquired and was used for genotyping with high

density SNP arrays.

### **The INGI-Val Borbera study (INGI\_VB)**

The INGI-Val Borbera population is a collection of 1,785 genotyped samples collected in the Val Borbera Valley, a geographically isolated valley located within the Apennine Mountains in Northwest Italy.

### **The Lothian Birth Cohort 1921 (LBC1921)**

LBC1921 consists of 550 (234 male) relatively healthy individuals, assessed on cognitive and medical traits at a mean age of 79.1 years (SD = 0.6). They were born in 1921, most took part in the Scottish Mental Survey of 1932, and almost all lived independently in the Lothian region (Edinburgh City and surrounding area) of Scotland. Data on alcohol intake is available.

### **The Lothian Birth Cohort 1936 (LBC1936)**

LBC1936 consists of 1091 (548 male) relatively healthy individuals who underwent cognitive and medical testing at a mean age of 69.6 years (SD = 0.8). They were born in 1936, most took part in the Scottish Mental Survey of 1947, and almost all lived independently in the Lothian region of Scotland. Data on alcohol intake is available.

### **The Northern Swedish Population Health Study (NSPHS)**

The NSPHS was initiated in 2006 to provide a health survey of the population in the parish of Karesuando, county of Norrbotten, Sweden, and to study the medical consequences of lifestyle and genetics. This parish has about 1,500 inhabitants who meet the eligibility criteria in terms of age ( $\geq 15$  years), of which 1066 individuals participated in the study.

### **The Orkney Complex Disease Study (ORCADES)**

The Orkney Complex Disease Study (ORCADES) is a family-based study of 2078 individuals with ancestry from the isolated Scottish archipelago of Orkney. Fasting blood samples were collected and over 300 health-related phenotypes and environmental exposures were measured in each individual. All participants gave informed consent and the study was approved by Research Ethics Committees in Orkney and Aberdeen.

### **The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)**

All data come from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). A detailed description of the study has been published elsewhere. PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5,804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements.

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