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Genetic Sum Score of Risk Alleles Associated with Body-Mass-Index Interacts with Socioeconomic Status in the Heinz Nixdorf Recall Study

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Content

1 Introduction

Although societies of developed countries have never been healthier and life expectancy has never been higher, social inequalities in health among and within countries are still persisting and remain a key public health problem (Marmot and Siegrist, 2010). The past 30 years of epidemiologic research provided ample evidence that the distribution of health and disease is not arbitrary; it rather follows a social gradient and changes depending on social, economic and cultural factors. This means that the highest health risks and shortest life expectancy are experienced by those with the least amount of independent availableness of economic, cultural and social resources, as shown in various studies (Helmert et al., 1989; Hurrelmann et al., 2011; Mackenbach et al., 2008; Marmot, 2005).

The disease burden of obesity[1], for example, remains high in developing but also in economically developed countries. It has been estimated that in 2015 4.0 million deaths worldwide were caused by a high body mass index (BMI) (Afshin et al., 2017). The World Health Organization (WHO) recognized obesity as an epidemic (Herrera and Lindgren, 2010) and reports an obese proportion of 23.3% men and 23.9% women in the German population aged 18-79 years (data collected 2008-2011) (World Health Organisation, 2013). Prevalence forecasts predict that obesity rates are still on the rise which will continue to contribute to morbidity and mortality in upcoming years (Boccia et al., 2014; Mensink et al., 2013). This will impose a great economic burden on the healthcare systems in the future (van Dieren et al., 2010; Zhang et al., 2010), as obesity is a prevalent risk factor for other non-communicable disorders such as diabetes mellitus type 2 and cardiovascular disease.

Several factors such as economic growth, urbanization and changes in lifestyles, as a result of modernization (e.g., higher consumption of calories, fats and sugars on the one hand and decreased physical activity on the other hand), are mentioned as leading causes of obesity (van Vliet-Ostaptchouk et al., 2012). Also, epidemiologic research has shown that a lower socioeconomic status (SES) is strongly associated with a higher prevalence of obesity, especially in westernized countries (Everson et al., 2002; McLaren, 2007; Wardle et al., 2002; Wu et al., 2015). Nevertheless, obesity is a complex condition influenced not only by various environmental and behavioral factors, but also by genetic variants (Albuquerque et al., 2017;

[1] A commonly used surrogate marker for obesity is the body mass index (BMI) which, according to the WHO, classifies a person with a BMI ≥ 30 kg/m² as obese (World Health Organization, 2000).

Bochud and Malats, 2011; Mackenbach, 2006) and people seem to respond differently to their psychosocial environment due to their genetic predisposition (van Vliet-Ostaptchouk et al., 2012). Evidence for a genetic contribution to the risk of obesity is delivered by genome-wide association studies (GWAS). A variant of the fat mass and obesity-associated *FTO* gene as well as a variant near *MC4R* became well established and thoroughly replicated common genetic risk factors for obesity (Andreasen and Andersen, 2009). The latest meta-analysis of GWAS, carried out by the Genetic Investigation of Anthropometric Traits (GIANT) consortium, found 97 single nucleotide polymorphisms (SNPs) strongly associated with BMI (Locke et al., 2015). However, these loci have only small individual effects on BMI and together only explain 2.7% of the BMI variance (Albuquerque et al., 2017; Locke et al., 2015).

The so far unexplained variance of BMI may partly be explained by interactions between genes and the environment (GxE), meaning that a certain environmental exposure changes the effect of some genetic variants (Qi and Cho, 2008; Winham and Biernacka, 2013). As the exposure to several obesogenic and environmental risk factors or behaviors is more prevalent among groups of lower SES (Ball et al., 2002; House et al., 1994; Pampel et al., 2010; Schmidt et al., 2017), SES indicators can be used to mark differing environmental conditions (Schmidt et al., 2017). Twin studies have suggested that the SES modifies the genetic effect on BMI; Education was found to be interacting with genetic influences on BMI (Johnson et al., 2011) and income on overall physical health (Johnson et al., 2010; Johnson and Krueger, 2005), demonstrating gene by SES interaction (GxSES).

Despite an increased number of researches in this area in the past years, empirical studies examining GxSES on BMI incorporating genome-wide molecular genetic information are limited. In response to this, the present thesis is intended to improve the understanding of gene-environment interaction to examine whether unequally distributed resources influence the genetic susceptibility to higher weight within a population-based cohort.

Thus, possible interactions between a BMI-related genetic risk score and education and income, as indicators of SES, on BMI will be evaluated. As certain environmental, psychosocial and, in particular, lifestyle behaviors are often present in groups of lower SES which form important risk factors for a high BMI as they lead to an excess body fat accumulation, they are contributors to the high prevalence of obesity. Therefore, this thesis further intends to evaluate whether such SES-related health behaviors (i.e., alcohol consumption, physical activity and tobacco smoking) have a mediating effect on the interaction between genetic variants and the environment.

This thesis will be structured as follows: To begin with, a theoretical part will give insights into basal concepts and explanatory approaches of social inequality in health and provide background information on genetics and disease and on gene-environment interactions (chapter 2). After a description of materials and methods used in the empirical part of this work (chapter 3), results of association analyses will be presented (chapter 4). Last, results will be discussed and related to the theoretical considerations and suggestions for further research will be provided (chapter 5).

2 Theoretical concepts

2.1 Socioeconomic status, social inequality and health

The term *social status*, or the more neutral concept *socioeconomic status (SES),* which will be used throughout this thesis*,* describes the individual position of a member of a society in a social structure that is characterized by social inequality. The SES is commonly assessed by the indicators education, occupational status and income, either individually or as a multidimensional aggregated index (Jöckel et al., 1998; Lampert, 2016). Although these measures are moderately correlated, e.g., a good education is associated with an adequate occupational status and thus a higher income, they are distinctive core dimensions of *vertical social inequality* and each of them represents certain aspects of social position. They further allow the subdivision of the population in top and bottom and thus form the basis for the hierarchical structure of society (Hernandez and Blazer, 2006; Mielck, 2011), but influence health and health behavior in diverse ways due to their different characteristics. In literature, several causal pathways have been described in which higher levels of education and income can affect health outcomes: higher education leads to more knowledge and skills promoting health (such as healthy behaviors), improved health literacy[2] and a greater sense of control. A higher income enables people to purchase adequate goods and services (e.g., better nutrition, access to health care services and medicine), people are more likely to live in safer and advantaged neighborhoods (e.g., less air pollution, better communities, safety) and might feel a greater sense of control over their own environment (Hernandez and Blazer, 2006). The occupational status, and its influence on health and health behavior, is mostly discussed with regard to health-related working conditions; people with a low status job tend to be more exposed to stress, pollution or higher physical demands at the workplace (Galobardes et al., 2006). These indicators make it possible to reflect someone's social status at different times in life. As highest educational attainment and years of full-time education only change little over adulthood and remain unchanged in most cases (education is usually completed before detrimental health effects occur in adulthood), the likelihood of reverse causation is reduced when using education as a measure of SES (Shavers, 2007). Moreover income has a cumulative effect over the life course and can change most on a short term basis (Galobardes et al., 2006).

[2] Health literacy has been defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (Ratzan and Parker, 2000, page vi).

While the concept of vertical social inequality describes social class-specific differences, the expression of horizontal inequality refers to differences in socio-demographic characteristics. These dimensions, e.g., age, gender, family status and nationality cut across the boundaries of vertical social inequalities and are referred to as *horizontal social inequalities*. They follow a certain distribution within each social class and do not permit hierarchization (Hradil, 1987; Mielck, 2005, 2011; Richter and Hurrelmann, 2009).

The SES, the core dimension of vertical social inequality, does not directly affect the health status. The influence is rather indirect and is mediated by other factors which are unequally distributed among a population, but are interlinked in their effect on health: material, psychosocial and behavioral factors (Mackenbach, 2005; Richter and Hurrelmann, 2009) (Figure 1).

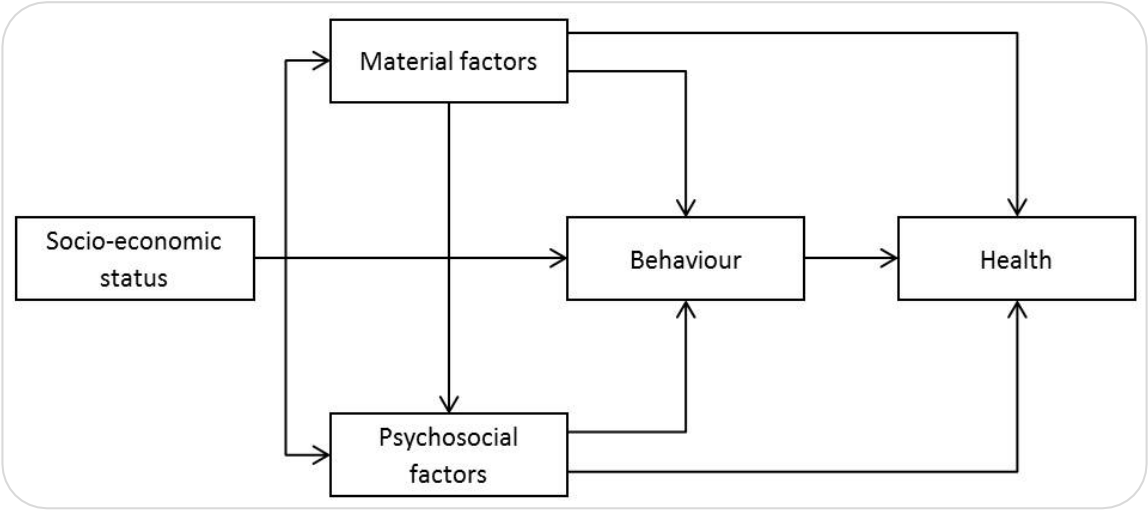

Figure 1 Explanatory diagram of factors, which 'mediate' between low socioeconomic position and risk of ill health (Mackenbach, 2006, p.23).

The social gradient therefore consists of social unequally distributed material living conditions, such as different income situations or different housing and working conditions. Material factors include determinants linked to the physical environment, e.g., housing conditions, food and other resources, which can have a direct impact on health but may also affect health through other mechanisms such as risk-taking health behaviors (smoking, alcohol consumption etc.).

Other determinants contributing to the concept of health inequalities are psychosocial factors. This emphasizes that people with a low SES experience more psychosocial stress, social exclusion, low social support or discrimination. Psychosocial factors can lead to ill health, either through biological pathways or through health damaging behaviors. This shows the interrelationship of the three conditions which each influence health through specific biological factors and might not only affect exposed people but also their offspring (Hedinger, 2016; Lampert, 2016; Mackenbach, 2005; Mackenbach, 2006; Marmot and Siegrist, 2010).

Thus, social inequality does not refer to an absolute undersupply, but rather to an unequal distribution of scarce and coveted tangible and intangible resources (including unequal access towards them) among members of a society, which affect the realization of certain life goals and with it the quality of life of individuals. In this sense, some populations or population groups are always disadvantaged, in both, poorer and richer states (Mielck, 2011; Steinkamp, 1993). To describe the relationship between social inequality and health, the terms *social inequalities in health* or *health inequalities* have gained acceptance (Hurrelmann and Richter, 2009; Jöckel et al., 1998; Tiesmeyer et al., 2008).

2.1.1 Explanatory approaches of health inequalities

Classical debates on the causation of health inequalities, which are essentially built on the Black Report[3] (Black and Townsend, 1986), focused on explanatory approaches based on two conflicting causalities that have not lost their relevance to date. In recent years, much research has been conducted to further describe and explain why health inequalities still persist despite the welfare state. Although several comprehensive explanatory models were developed, no unified explanatory theory has been stated so far (Hedinger, 2016; Lampert, 2016).

According to the *social causation hypothesis,* the main explanatory approach, the health status is influenced by the SES of a person (Mackenbach, 2006). In this approach, the SES does not affect the health status directly, but indirectly through socioeconomic differences related to material, or structural resources (such as income and occupational position), psychosocial resources and health-related behavior (Elkeles and Mielck, 1997; Mackenbach, 2006). Accordingly, population groups with a high SES have a favorable health effect, while groups of

[3] The Black Report was the summarized result of a British group of scientists who conducted, under the lead of Sir Douglas Black, empirical analyses on social differences in morbidity and mortality in Britain 1977.

low SES are to a greater extent affected by unfavorable living and working conditions (upper part of Figure 2).

Contrary to this, another explanatory approach is concerned with health during early life and its relationship between social mobility and health in later stages of life (Blane et al., 1993). In social epidemiology, this process is referred to as *direct social selection* or *drift hypothesis*. It attributes the existence of socioeconomic differences back to the selection processes. This approach assumes health-related social mobility in which people with poor health have a higher probability to experience a social decline than healthier people as they are less likely to finish high level education and obtain high occupational positions, i.e., poor health leading to a lower SES (Elkeles and Mielck, 1997). It thus accepts a causal relationship between social position and health but in reversed direction.

The direct selection hypothesis was extended by the concept of *indirect selection* which states that social mobility processes are not facilitated directly through the health status, but rather indirectly through a third variable; certain (health) determinants that cause variation in health and the SES (Blane et al., 1993). Early studies have found that health-related selection does exist in the explanation of socioeconomic attainment, however, only to a small extend (Mackenbach, 2005; McCartney et al., 2013) (lower part of Figure 2).

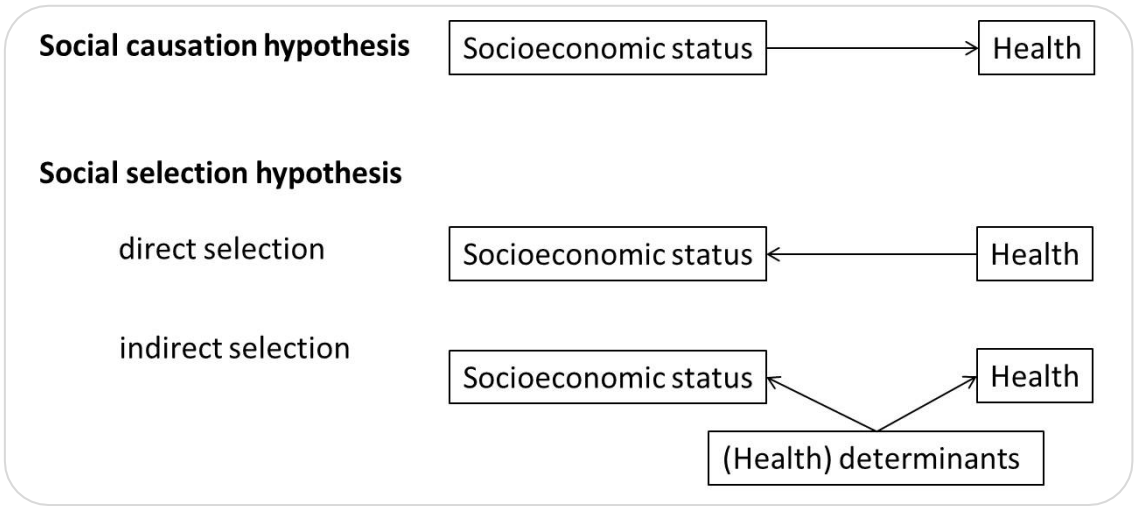

Figure 2 Overview of explanatory approaches of health inequalities (own illustration based on Elkeles and Mielck, 1997 and Mackenbach, 2006).

Cohort studies established another explanatory approach, which integrates the previously presented approaches: the *life course perspective*. This perspective integrates different concepts into one framework and claims that the health status in later life is determined by a combination of different factors which change over time while this approach also takes account of conventional risk factors, such as smoking and hypertension (Dragano and Siegrist, 2009; Kuh et al., 2003; Mackenbach, 2005). Thus, the approach recognizes the factor time in understanding long-term causal relationships between exposures and outcomes (Lynch and Smith, 2005). Inequalities in health in early life stages and in utero can have an impact on health in later life, regardless of subsequent life events (Kuh and Ben-Shlomo, 2007; Smith, 2003). Early life conditions influence habits in early childhood, which manifest in health impacting choices in later adulthood. Last, such a long-term exposure to health affecting conditions might amplify the health effects (Arcaya et al., 2015). This perspective clarifies that the health of humans is the product of an interaction of biological and social influences at different stages of life (Dragano and Siegrist, 2009).

2.2 Genetics and diseases

2.2.1 DNA - Carrier of genetic information

Every human is unique and human traits are not only shaped by the environment but also by the individual genetic basis. The extent and nature of genetic variations go along with different consequences ranging from physical appearance to risk of disease (Knight, 2010). The nucleus of every human cell (except for gametes and red blood cells) carries the individual's own genetic information in 46 chromosomes or 23 pairs - 22 pairs of autosomal chromosomes and a pair of gonosomes, the sex chromosomes. Females have two copies of the X chromosome, while males have one X and one Y chromosome. Chromosomes are composed of spooled deoxyribonucleic acid (referred to as DNA) and proteins and vary in size. DNA can be seen as the genetic blueprint as it carries all genetic information needed to control the production of proteins, which are essential for an organism to develop and live. The DNA is a spiral staircase-shaped double-stranded helix consisting of two strands formed from sugar-phosphates backbones and four distinct bases: adenine (A), cytosine (C), thymine (T) and guanine (G). The two strands of DNA are held together by a pair of bases (bp), one from each strand, which are connected by hydrogen bonds. The bases are complementary and do not pair randomly: A only pairs with T, and C only pairs with G. One base, one phosphate molecule and the sugar molecule deoxyribose form one nucleotide (Figure 3). Genes consist of long strings of nucleotides and are the functional unit of DNA. The location of a gene or any specific DNA sequence on a chromosome pair is called a locus. Genes and the base pairs within each gene, encode for twenty different amino acids needed for the production and regulation of proteins. According to the one-gene-one-polypeptide hypothesis each gene codes for the production of one protein, multiple genes may synthesize the same protein. Proteins are complex molecules, which determine the structure and functions of the body's cells. In addition to the genes for protein synthesis, the DNA also contains important information for other biological processes, for instance whether a gene is expressed - if there is a transcription at all - and in what quality and quantity proteins are synthesized. The overall genetic makeup is called the genotype (Knight, 2010; Laird and Lange, 2011; U.S. Department of Health and Human Services, 2010; Ziegler and König, 2010).

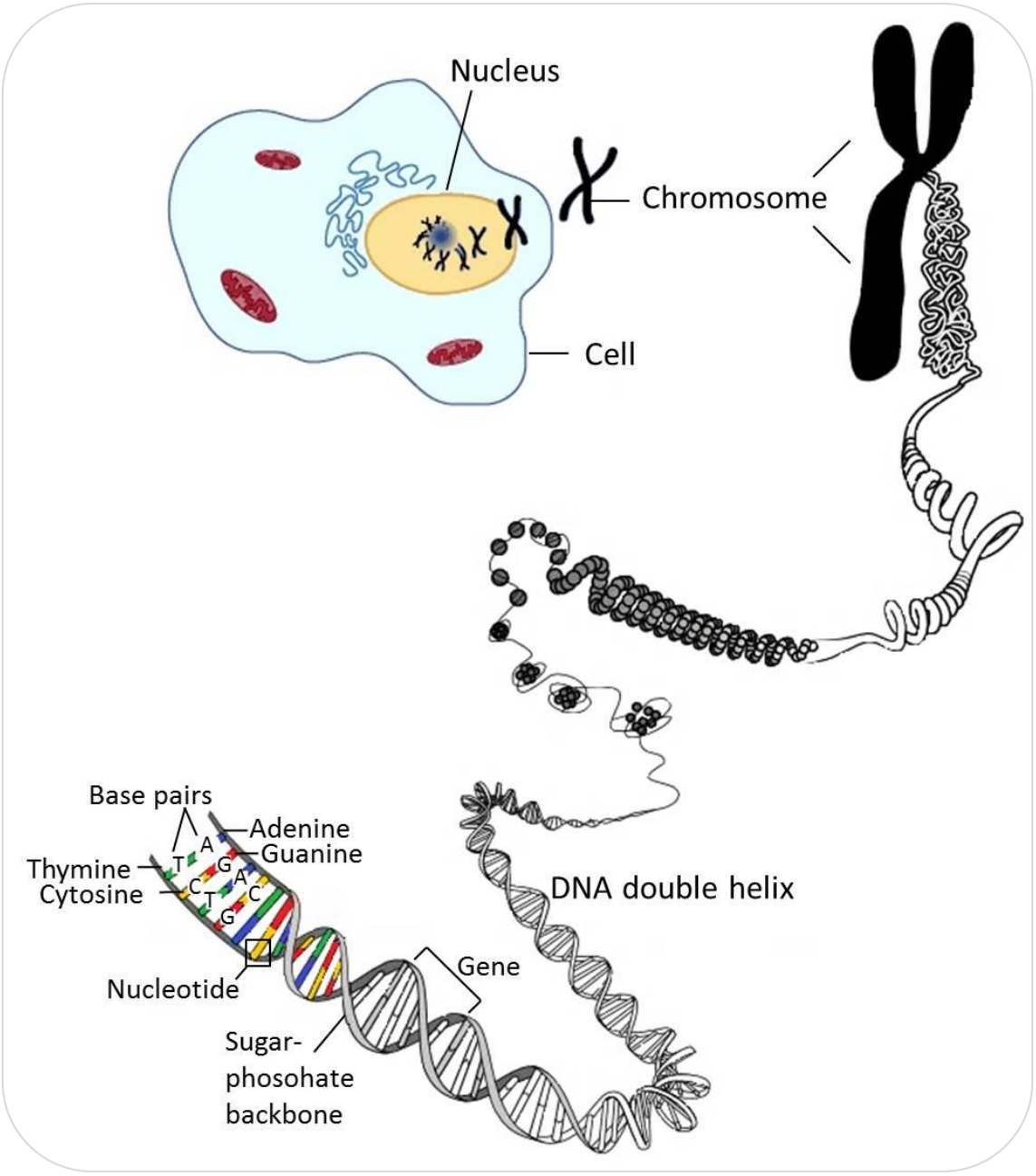

Figure 3 Structure of DNA and chromosomes (image adapted from Jorde et al., 1995, p.23).

Generally, all humans have the same genes, but not exactly the same DNA sequences. Variations arise due to mutations possibly occurring at many different levels, from large segments of chromosomes including multiple genes to single base pairs. Such variations in the DNA sequence have differing consequences, some having no effect at all, and others leading to disease (the phenotype), depending on their kind and location (Knight, 2010). In total, the entire human genome contains about 3.3 billion base pairs of which an average of 99.9% is arranged identically in two randomly selected persons. This means that only certain parts of the DNA have varying characteristics (one variant per 1,000 base pairs), which are also referred to as genetic polymorphisms (International HapMap Consortium, 2003). If two or more versions occur for a polymorphism, one speaks of different alleles at this position of the DNA strand. As every human has a double set of chromosomes, two variants for each polymorphism exist. If these two are identical on both DNA strands the individual is called homozygous and heterozygote if the alleles differ. The frequency of alleles in a certain population is named allele frequency. A minor allele frequency (MAF), the frequency of the rarer allele, of at least 1% defines a polymorphic variation (common variant) while a MAF below 1% is referred to a mutation (rare variation) (Bodmer and Bonilla, 2008; Jorde et al., 1995; Ziegler and König, 2010).

Single nucleotide polymorphisms (SNPs) are the most common form of variation in the genome and make up 90% of the variation in the population (International HapMap Consortium, 2003). SNPs are a variation at one single base of a DNA sequence. For example, some people may have the sequence **A A A C T** (read from left to right on the top strand) while the corresponding sequence in others is **A A G C T** at the same locus. The two sequences differ at the third base pair, where an A base is substituted for a G (Figure 4) (Camp and Trujillo, 2014; Laird and Lange, 2011). Most SNPs are found in non-coding regions. Less than 1% of all SNPs results in a variation in proteins, however, some of them are located in genes or in the promoter region of genes and can therefore be directly viewed as a candidate for a causal variant of disease (Venter et al., 2001; Ziegler and König, 2010).

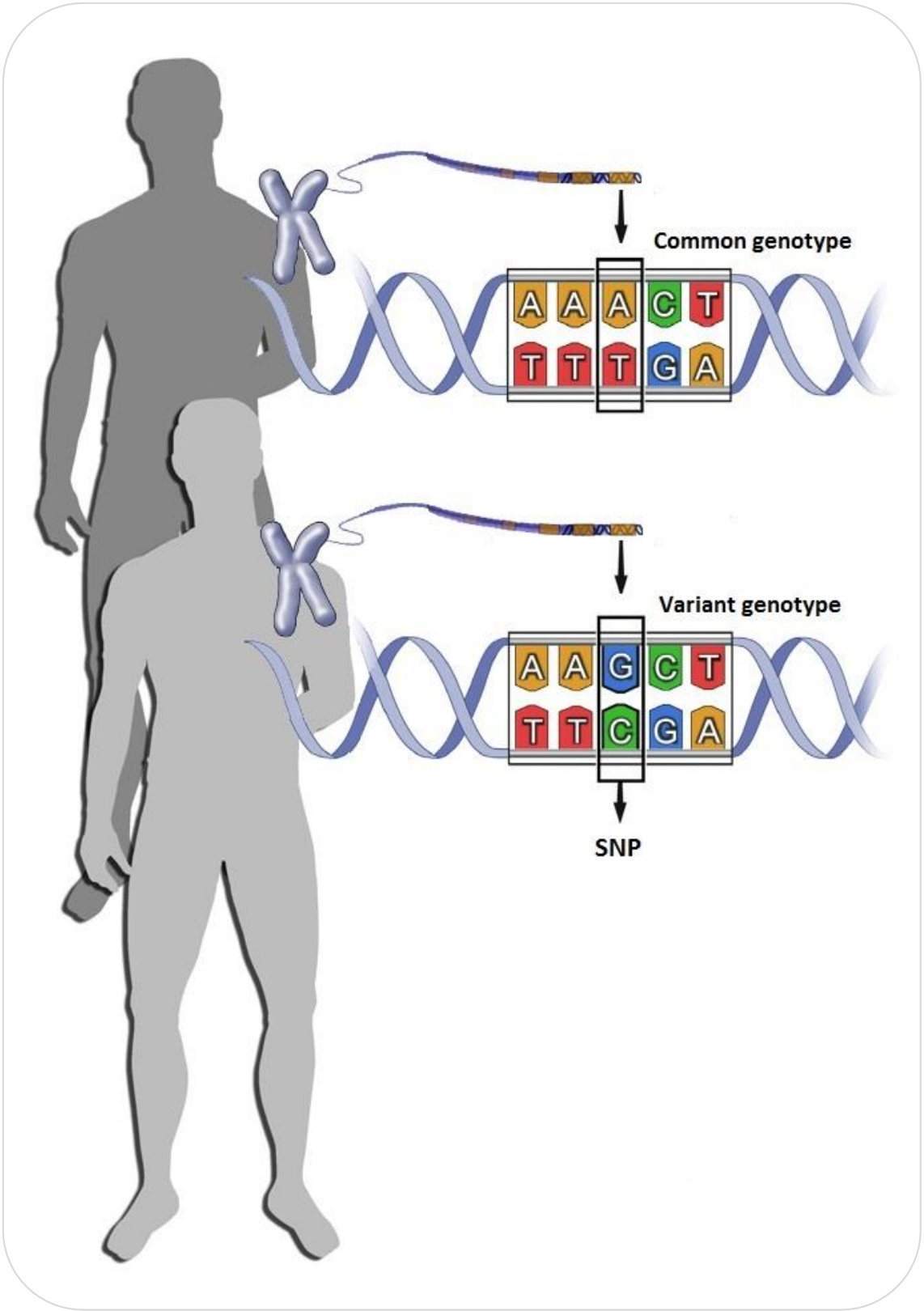

Figure 4 Illustration of a single nucleotide polymorphism (SNP) (image altered from Camp et al., 2014, p. 301).

2.2.2 Genetic disorders

Genetic disorders can roughly be grouped into three categories: chromosome disorders, monogenetic disorders and multifactorial inheritance disorders (polygenetic disorders). Chromosome disorders are caused by genome mutations occurring during cell division, in which segments of the chromosomes may get lost (deletion), identical segments of the chromosome get added to the normal chromosome (duplication), chromosome parts break apart and get rejoined in a different order (inversion), or a segment of one chromosome may be exchanged and translocated with a pair of another chromosome. Latter can lead to a variation of the total number of chromosomes (Ziegler and König, 2010). Examples of chromosome disorders are the Down Syndrome which is caused by trisomy 21, three copies of chromosome 21; or the Klinefelter Syndrome, caused by two copies of the X chromosome and one of the Y chromosome (National Human Genome Research Institute, 2015). Monogenetic disorders are usually caused by a polymorphism in coding areas of the DNA, which risk allele leads to a direct structural or functional change in the synthesized protein. Examples of monogenic disorders are sickle cell disease, cystic fibrosis and Huntington disease, which are relatively rare and inherited in a Mendelian fashion. Most genetic disorders are, however, much more complex and based on polygenic impact. They are multifactorial inherited, i.e., they are caused by a combination of several different polymorphisms and environmental factors. Examples of such multifactorial disorders are diabetes mellitus type 2 and heart diseases (National Human Genome Research Institute, 2015).

2.2.3 Genome-wide Association Studies

Studies aiming at uncovering genetic predispositions to diseases attempt to demonstrate an association between genetic risk factors and complex diseases. Two main approaches can be distinguished: Candidate gene studies, in which a small number of genes and genetic markers are being considered and genome-wide association studies (GWAS) covering the entire genome in a large number of human subjects (Bickeböller and Fischer, 2007). GWAS are referred to as hypothesis-free, as their applicability does not require any prior knowledge of the genetic causes of the disease being studied. Rather, polymorphisms for GWAS are selected in such a way that they uniformly cover the entire genome and are sufficiently frequent to enable reliable statistical statements regarding their relationship to a disease (Krawczak, 2014). A positive

association identifies a genomic region that might be involved in the development of a disease and arises when a genetic variant is more frequent in individuals with a disease than in unaffected individuals. Based on the assumption that one million independent variants are being tested simultaneous, the threshold for statistical significance in a GWAS, after Bonferroni correction for multiple testing, is a p-value below and equal $5*10^{-8}$. To detect small to moderate effect sizes for complex traits, high sample sizes are needed. As this is often lacking in single GWAS, meta-analyses of GWAS are being used to pool the data to increase sample sizes and statistical power (Ziegler and König, 2010).

GWAS were enhanced by scientific and technological developments. The completion of the Human Genome Project in 2003 (https://www.genome.gov/hgp/) established the first full map of all human genes, covering 1.4 million SNPs of the human genome (National Human Genome Research Institute, 2016). Further, the International HapMap Project in 2005, identified genetic variants in the human genome across multiple ethnic populations and established linkage disequilibrium (LD) patterns of haplotypes, a sequence of highly correlated SNPs (International HapMap Consortium, 2003, 2005). These form so-called haplotype blocks, which are simultaneously passed onto the next generation (Schaid et al., 2018). The LD describes the non-random relation between these SNPs and the more frequent the recombination in the course of reproduction between them is to be expected, the lower the LD. Identifying a set of such polymorphisms makes it possible to reconstruct most of the genome-wide variability by using carefully selected tag SNPs; i.e., SNPs that adequately represent not only itself but also the haplotype block in which they are located. After the completion of the HapMap project, microarray SNP-chips were developed that make use of these tag SNPs which made it possible to lower the number of common variants on the chip and still predicting up to millions of SNPs using imputation. Such chips enable to measure the genotype of hundreds of thousand defined SNPs for each subject. The ‘metabochip’, for example, was established as a genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits that assays variation in nearly 200,000 sites in the human genome (Voight et al., 2012).

2.3 Gene-environment interactions

For a long time it was regarded as certain that diseases are shaped on the one hand by influences of the environment (such as the SES) and on the other hand by genes, independently of one another. However, studies show that genes and the environment are closely linked and an interplay of these factors leads to different expressions of genetic variation conditioning on environmental factors (Liu and Guo, 2015). Heritability studies involving environmental exposures among twins suggested a shared influence of genetics and the environment in shaping a disease (Johnson et al., 2010; Johnson and Krueger, 2005), implying gene by environment interaction (GxE). Recently, a rapidly growing number of empirical studies have demonstrated modifications of a genetic effect by environmental factors considering findings of GWAS. A variant of chromosome 9p21.3 was, for example, found to be modified by SES to influence coronary artery calcification and incident coronary events (Schmidt et al., 2017). Exposure to certain environmental factors can influence the effect of genetic predisposition, and the effects of the environment can be modified by genetic predisposition (Ottman, 1996; Rothman et al., 1980). It can thus be hypothesized that genetic influences do not have the same effect on everyone universally, but differ between social groups, situations and societies.

In a public health perspective gene-environment interaction describes the dependence of an outcome on the simultaneous occurrence of two factors (Rothman et al., 1980). Detecting the presence of GxE is done by measuring if the combined effect of one or more genes with one or more environmental factors on a given phenotype is greater (or smaller) than the sum of their marginal effects. Figure 5 illustrates the underlying logic of such a GxE interaction in a simplified way: the upper part of the figure shows that a hypothetical genetic variant embedded in a low-risk environment (high SES) does not lead to the phenotype (indicated by the dotted line), while a clear relationship towards the phenotype (indicated by the thick black line) is seen between the same genetic variant within people living in a high-risk environment (low SES), shown in the lower part of the figure.

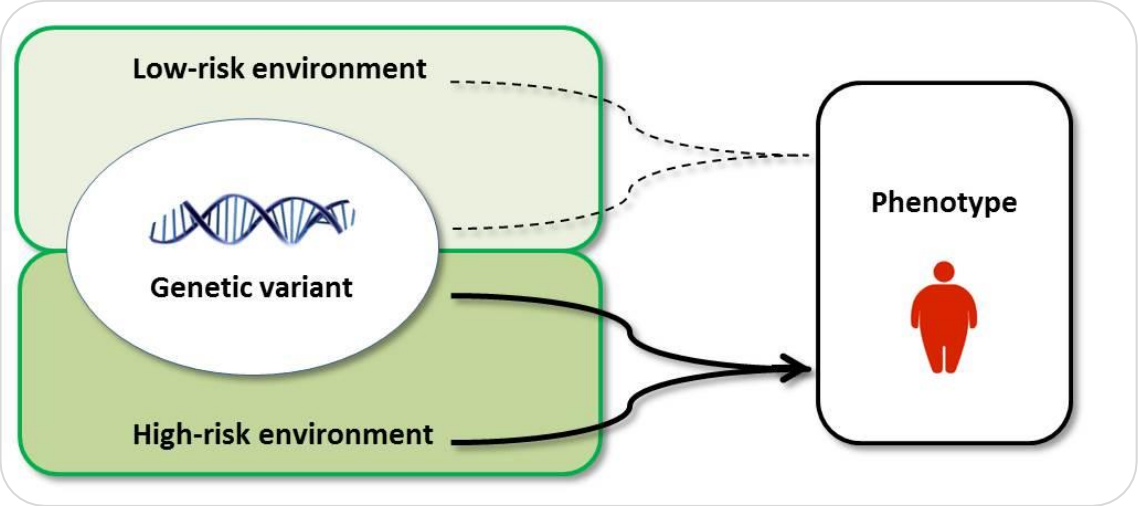

Figure 5 Simplified presentation of the concept of a gene by environment interaction (own illustration).

Given the fact that certain environments influence the effect of the size of a genetic predisposition to a certain phenotype, studying GxE interactions can give deeper insights into disease causing mechanisms. By demonstrating which factors increase or decrease the genetic susceptibility and by identifying subgroups of individuals for whom risk factors are most relevant, public health interventions can be optimized as health interventions and treatment selections can be targeted to those at risk (Thomas, 2010). This will reduce both, social and economic costs of health interventions (Mangum and Mangum, 2018). Also, GxE research might lead to a profounder knowledge on patterns of inheritance that shed light on mechanisms that cause inequalities in health among some individuals and population groups (Goldenberg et al., 2013).

Consequently, it can be hypothesized that the social causation theory of explaining inequalities in health has to be extended by the concept of gene-environment interaction. Meaning that the effect of genetic variants on complex disease outcomes, such as obesity, may be of different size or of different effect direction across SES groups, and modified by the SES through its underlying unequally distributed factors (material, psychosocial and behavioral) (Figure 6).

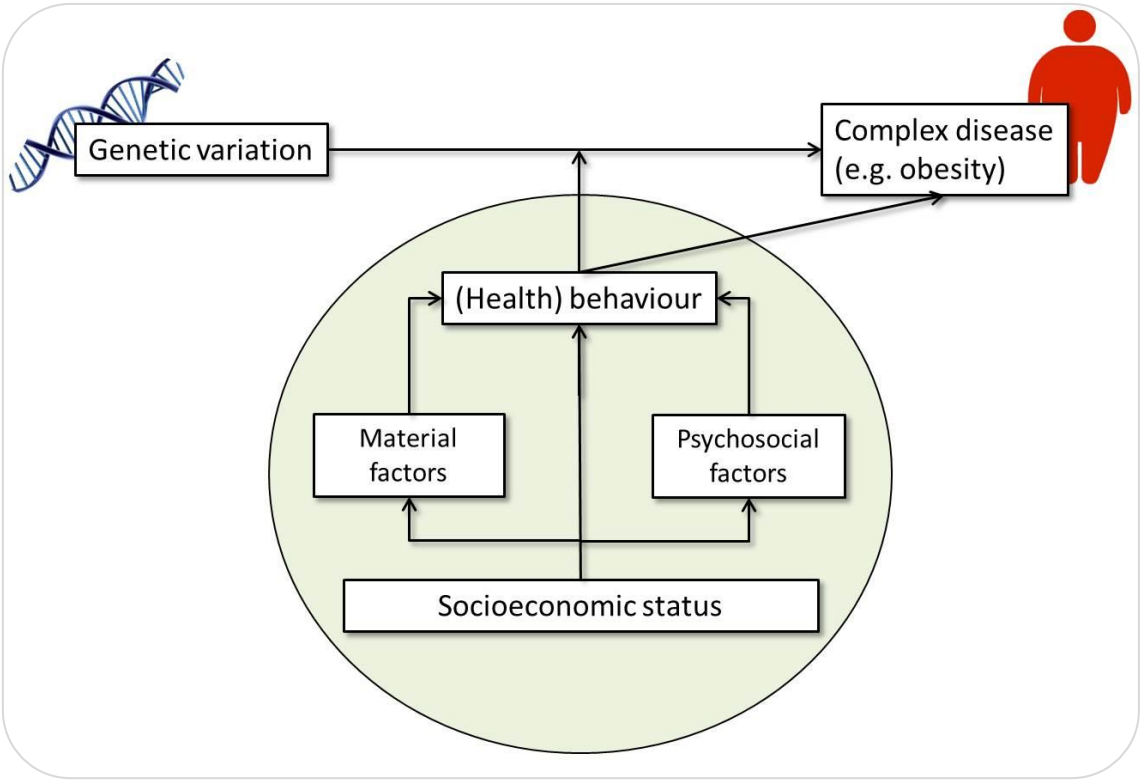

Figure 6 Expansion of the social causation theory by gene-environment interaction (own illustration based on Mackenbach, 2006, p.23).

3 Material and methods

3.1 Study population

For analyses, data of questionnaires, anthropometric measurements and on genotyping of the baseline examination of the Heinz Nixdorf Recall Study (HNR) were used. Recall is an acronym and stands for risk factors, evaluation of coronary calcification, and lifestyle. The baseline examination took place from December 2000 until June 2003 and the recruitment efficacy proportion was 55.8%. The Recall study is a population-based prospective cohort study which aims to improve the predication of cardiovascular events in the general population. In brief, 4814 men and women aged 45-75 years were enrolled, who were randomly selected from mandatory registries of residence in the cities Bochum, Essen and Mülheim/Ruhr within the Ruhr region (Ruhrgebiet) in North Rhine-Westphalia, the largest metropolitan area in Germany. The majority of the study population is of Central European origin (Schmermund et al., 2002).

The study was approved by the local ethics committees, and included extended quality management procedures and recertification according to DIN ISO 9001:2000. Informed consent was obtained from all participants.

3.2 Data collection and variable definitions

3.2.1 Body mass index (BMI)

At study baseline, BMI was assessed as a proxy measure of obesity. BMI was calculated as weight (in kilograms), measured in underclothes, divided by the square of the height (in meters) (BMI= kg/m^2).

3.2.2 Indicators of socioeconomic status (SES)

Education and income were assessed as two separate indicators of SES. Participants of the Heinz Nixdorf Recall study answered questions on their educational attainment and household income in standardized computer-assisted face-to-face interviews at study baseline. Education was defined by combining school and vocational training as total years of formal education according to the International Standard Classification of Education (ISCED). For statistical analyses,

education was inserted as a continuous variable or was categorized into four educational groups with 10 years or less years, 11 to 13 years, 14 to 17 years and 18 or more years of education. The lowest educational group is equivalent to a minimum compulsory school attendance and no additional vocational degree, while the highest educational group of 18 and more years of education is equivalent to a vocational training including additional qualification or a university degree.

Income was measured as the monthly household equivalent income. It was calculated by dividing the total household net income by a weighting factor for each household member according to criteria of the Organization for Economic Co-operation and Development (OECD), the so called 'OECD-modified scale' (Hagenaars A, de Vos K, Zaidi MA). Using the household income rather than the individual income enables to take account of the different sizes and compositions of households. This indicator was included as a continuous variable or divided into four groups, using sex-specific quartiles as cut-points.
The transformation of the indicators made them internationally comparable. Both SES indicators were analyzed separately to account for their different mechanisms in causing health inequalities (Galobardes et al., 2006; Geyer et al., 2006).

3.2.3 Indicators of SES-related health behavior

Physical activity, smoking status and alcohol consumption were further assessed in face-to-face interviews at baseline and were included into the present study to represent SES-related health behaviors. Information on physical activity was obtained asking about engagement in physical exercise during the past four weeks and was then dichotomized as no exercise versus exercise one and more times per week depending on the response. Current smoking was defined as smoking cigarettes during the past year, former smoking as having a history of smoking before the past year and never smoking as never having smoked. Smoking status was dichotomized for analyses with current smoking versus former plus never smoking. Amount of alcohol consumption was estimated from questions on the total number of alcoholic drinks and by type of drink (beer, wine, sparkling wine, and spirits) consumed in a week and is given in gram per week (g/week). Alcohol consumption was inserted as a continuous variable into analyses.

3.2.4 Genetic Data

Lymphocyte DNA was isolated from ethylene diamine tetra acetic acid (EDTA) anti-coagulated venous blood using the Chemagic Magnetic Separation Module I (Chemagen, Baesweiler, Germany). Genotyping was performed using different Illumina microarrays (Metabochip, Omni1, Omni1S, OmniExpress, HumanCoreExome; Illumina, San Diego, USA) according to the manufacturer's protocols. Genotyping on Metabochip was conducted on a total sample of n=4,570, of which 52 samples were excluded from data analysis because of gender inconsistency. Genotyping on the other chips was conducted on a total sample of n= 3,874 after quality control. Genotype imputation was carried out separately for each chip using IMPUTE v.2.3.0 (Howie et al., 2009), for Metabochip based on the reference sample 1000 Genomes Phase 1, March 2012 and for the other GWAS chips based on the reference sample 1000 Genomes Phase 3, October 2014.

Through the most recent meta-analyses of genome-wide association studies 97 SNPs representing independent genetic loci robustly associated with BMI ($p< 5 \times 10^{-8}$) were identified (Locke et al., 2015). 93 SNPs of these reported loci were extracted from Metabochip.
As the remaining four SNPs were not present on Metabochip, proxy SNPs were searched based on the concept of the linkage disequilibrium (LD). The proxy search was done with the web-based service of the Broad Institute SNP Annotation and Proxy Search[4] (SNAP) (Li et al., 2007), which is built on empirical observations from the 1000 Genomes Project (Johnson et al., 2008) .

Two proxy SNPs with an r^2 threshold[5] of ≥0.900 were both found on Metabochip:

- Proxy SNP rs17001561 was selected for SNP rs17001654 (r^2= 0.95) and
- Proxy SNP rs2035935 was selected for SNP rs16851483 (r^2= 0.90).

Two remaining SNPs

- rs9641123 and
- Proxy SNP rs9581855 selected for SNP rs12016871 (r^2= 1.0)

[4] http://archive.broadinstitute.org/mpg/snap/ldsearch.php, retrieved in October 2015
[5] The square of the correlation coefficient between two indicator variables r^2 is the most commonly used measure for linkage disequilibrium (LD) of biallelic markers (VanLiere and Rosenberg, 2008). R^2 ranges from 0 to 1, with 0 indicating no and 1 indicating complete LD, meaning highest correlation between two markers providing the same information.

were found in imputed data of GWAS Chips (Omni1Quad, Omni1S, OmniExpress, HumanCoreExome) in 3,874 subjects of the study population (Figure 7). The average certainty of best-guess for imputation was 0.97 for SNP rs9641123 and 0.98 for proxy SNP rs981855. Missing information for these two SNPs in the remaining 718 individuals was imputed using the Plink (v. 1.07) SNP scoring routine based on the sample allele frequency. Sensitivity analysis was conducted repeating the main statistical analyses after excluding these participants. As the results did not differ, results in the following are only reported for the main study population.

To assess genotyping error, Hardy-Weinberg equilibrium (HWE)[6] was tested for each of the 97 SNPs using Plink (v. 1.07). No deviation form HWE ($p<0.01$) was found.

Instead of testing single SNPs in their association to BMI, a BMI specific genetic risk score (GRS) was calculated by aggregating information from all SNPs. The advantage of using a GRS instead of just testing single SNPs is that as the number of SNPs included in a GRS grows, the distribution of values approaches normality, even when individual risk alleles are relatively uncommon (Belsky et al., 2013). Also, using a GRS minimizes the problem of multiple testing in single-variant analyses and maximizes statistical power (Liu and Guo, 2015). Therefore, an unweighted as well as a weighted GRS with BMI-associated SNPs were calculated. The unweighted score was calculated for each individual as the sum of BMI-associated risk alleles s_{ij} (0 for the non-risk homozygote state, 1 for the heterozygote state, or 2 for the risk homozygote state) at SNP *i* for each individual *j* across the selected 97 SNPs:

$$\mathbf{GRS_j} = \sum_{i=1}^{97} sij$$

The effect estimate of an association analysis with this variable can be interpreted as the average effect per additional risk allele. The BMI-associated risk alleles were additionally weighted by the corresponding effect size estimate of each SNP β_i reported in literature (Locke et al., 2015) for a weighted genetic risk score (wGRS):

$$\mathbf{wGRS_j} = \sum_{i=1}^{97} sij \ * \beta i$$

[6] Harold Hardy and Wilhelm Weinberg described that under certain assumptions (random mating, no selection of migration, no mutation, no population stratification and an infinite population size), allele and genotype frequency remain stable over generations within a large, randomly mating population and that there is a fixed relationship between allele and genotype frequency (Ziegler and König, 2010).

To reflect the number of BMI-increasing alleles, this weighted risk score was rescaled by multiplying the score by the number of variants and then dividing it by the sum of ß coefficients of the SNPs reported in the meta-analysis. A weighted risk score, however, does not have advantages over an unweighted risk score if the SNPs used for the score all have low effect size estimates which do not differ much or when their confidence intervals overlap. Due to this reason and as the effect size estimates obtained in the main analyses using the weighted GRS did not differ from the estimates resulting from the unweighted GRS (Table s-9, s-10 and s-11) results reported in this thesis will be based on the unweighted GRS.

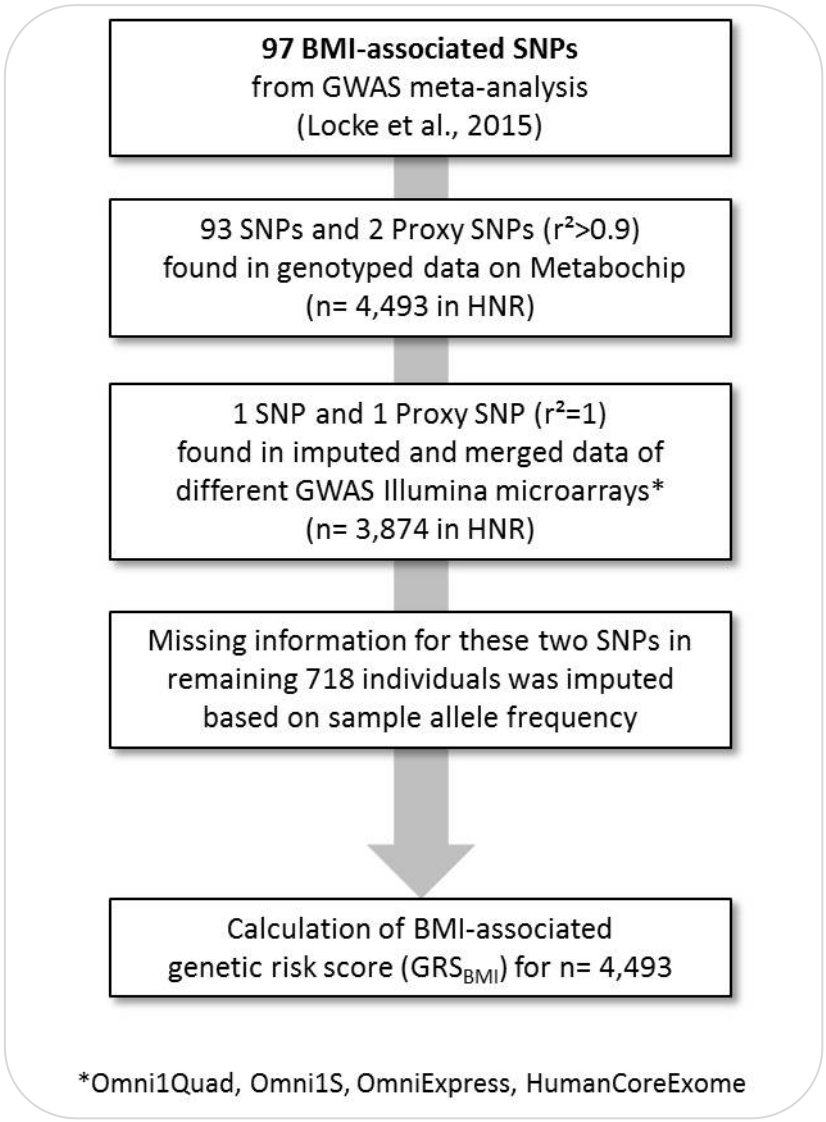

Figure 7 Flowchart of the selection of BMI-associated single nucleotide polymorphisms (SNPs) and calculation of genetic risk score (GRS) in data of the Heinz Nixdorf Recall Study (HNR) (own illustration).

3.3 Statistical analysis

3.3.1 Description of study population characteristics

The description of the study population characteristics regarding age distribution, number of BMI-associated risk alleles, BMI, obesity and indicators of SES was done stratified by sex. Continuous variables are reported as mean and standard deviation (±sd) or median and first quartile and third quartile. Discrete variables are given in frequency and percent.

Overall, 4493 participants with baseline information on BMI, gender, age and genetic data were included into analyses. Due to participants with missing data on education (n= 13; male= 10, female= 3), income (n= 279; male= 90, female= 189), smoking status (n= 76, male= 43, female= 33), physical activity (n= 71, male= 39, female= 32) and alcohol consumption (n= 109, male= 38, female= 71) respective analyses populations differed in the analyses (Figure 8). There were no differences in the essential characteristics between the subjects with missing values and the entire analysis population. Sensitivity analysis was conducted excluding participants for whom missing data were additionally imputed (n= 718). Effect size estimates of sensitivity analysis did not differ compared to results of analysis with main study population (Table s-8).

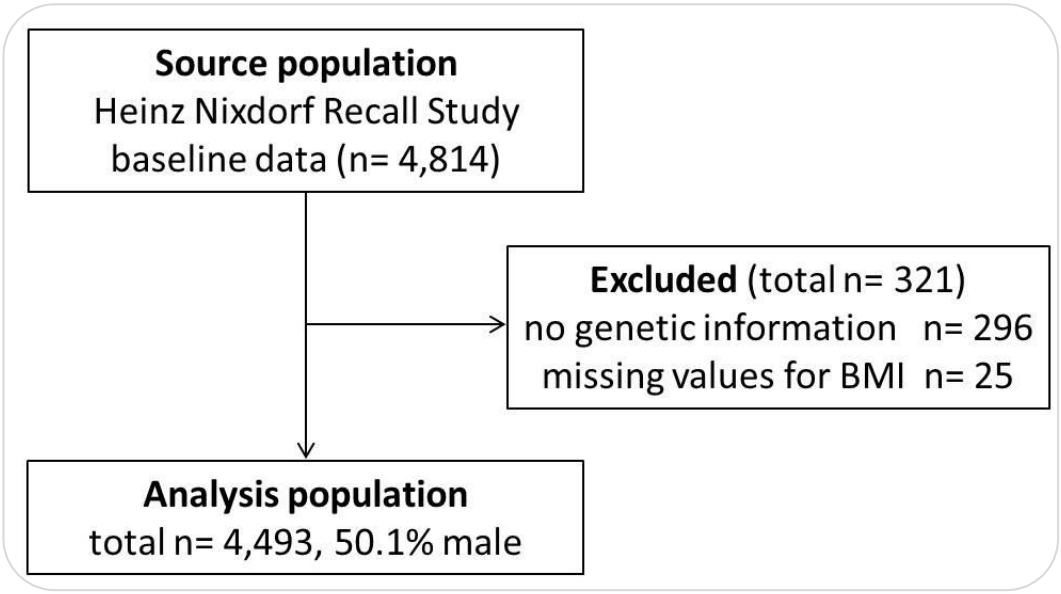

Figure 8 Flowchart of participants out of the entire HNR study cohort included in the analysis. BMI indicates body mass index (own illustration).

3.3.2 Association analyses

The different regression models of this thesis, which will be explained in the following, are displayed in the Table 1. To assess the association between SES indicators and BMI (model 1), linear regression models were fitted, adjusted for age and sex, as both indicators are negatively correlated with SES within the study population. Education and income were entered separately as continuous variables into regression models. Beta estimate (β) and 95% confidence intervals (95% CIs) of the association between income and BMI are displayed per additional 1000 Euros (€) and the association of education and BMI is given per one year of additional formal education. Linear regression models were further fitted to assess the association of the unweighted genetic risk score on BMI (model 2) and SES-related health behaviors (S) smoking, (PA) physical activity and (Alc) alcohol main effects with BMI (models 3-5), adjusted for age and sex. Again, beta estimates and their corresponding 95% CIs were calculated.

Association analyses of the genetic effect on BMI were calculated stratified by education groups, income quartiles, smoking status, physical activity and quartiles of alcohol consumption, adjusted for sex and age. The effect of SES indicators on BMI was further stratified by tertiles of the GRS, separately for income and education. Joint effects of the GRS and SES indicators on BMI were assessed by entering a dummy variable containing all possible combinations of GRS tertiles and SES groups, separately for education and income, into linear regression models using the group with the highest SES and lowest GRS as reference.

Possible interaction between the GRS and indicators of SES on BMI were assessed by entering the GRS, SES main effects and respective GRSxSES interaction terms into the models to calculate sex-specific and age-adjusted effect size estimates (model 6). Again, education and income were entered separately into the linear regression analyses. Literature states that in linear regression analyses the interaction coefficient means departure from additivity (Knol et al., 2007; Thomas, 2010), indicating that if the parameter of the gene-environment interaction effect ß=0 no interaction is present, while ß≠0 shows that the environmental exposure modifies the effect of the genetic variant(s) on the phenotype, and vice versa (VanderWeele and Knol, 2014; Winham and Biernacka, 2013).

To explore whether any interaction between the BMI-associated GRS and SES indicators was due to underlying interactions of SES-related health behaviors, smoking, physical activity and alcohol main effects and a respective, GRSxPhysical activity (GRSxPA), GRSxSmoking (GRSxS) or GRSxAlcohol consumption (GRSxAlc) interaction term as well as a respective SESxPhysical

activity (SESxPA) or SESxSmoking (SESxS) or SESxAlcohol consumption (SESxAlc) interaction term was included into model 6 (models 7-9), separately for each health behavior and SES indicator, adjusted for sex and age (Keller, 2014). In order to check for a possible confounding effect of SES on the GRSxPhysical activity, GRSxSmoking or GRSxAalcohol consumption interaction, the adjusted regression models 7-9 were fitted excluding SES variables and respective SES interaction terms (models 10-12).

Last, to follow up on the results of the main interaction analyses, further analyses of each of the 97 BMI-associated SNPs of the GRS were tested individually in their interaction with both SES indicators and the mentioned health behaviors on BMI were tested, including main effects and respective interaction terms in separate regression model, adjusted for age and sex. Effect size estimates of interaction analyses can be interpreted as the combined effect of SES indicators and each risk allele associated with BMI.

Table 1 Overview of the different linear regression models.

Model 1	BMI ~ SES + age + sex
Model 2	BMI ~ GRS + age + sex
Models 3-5	BMI ~ SES + PA/S/Alc + age + sex
Model 6	BMI ~ GRS + SES + GRSxSES + age + sex
Models 7-9	BMI ~ SES + GRS + PA/S/Alc + GRSxSES + GRSxPA/S/Alc + SESxPA/S/Alc + age + sex
Models 10-12	BMI ~ GRS + PA/S/Alc + GRSxPA/S/Alc + age + sex

Alc: alcohol consumption, BMI: Body Mass Index, GRS: genetic risk score, PA: physical activity, S: smoking, SES: socioeconomic status (income/education)

3.3.3 Implemented software

All statistical analyses were carried out with the statistical computing software R v3.1.1 (Statistical Computing Software R, 2011). The generation of the genetic risk score and the HWE tests were done with Plink v1.07 software package for Windows (Purcell et al., 2007). The internet based database of SNPs of the National Center for Biotechnology Information (ncbi) (http://www.ncbi.nlm.nih.gov/snp) was used to get more detailed information on the various SNPs. The proxy search was done with the web-based service of the Broad Institute SNP Annotation and Proxy Search (SNAP) (http://archive.broadinstitute.org/mpg/snap/ldsearch. Php, retrieved October 2015).

4 Results

4.1 Description of study population characteristics

Of 4814 participants of the Heinz Nixdorf Recall study, 4493 participants with non-missing data on BMI and genetic information were included into the present study, of which 2242 (49.9%) were female. Baseline characteristics of the study population are displayed in Table 2.

Table 2 Characteristics of study population, stratified by sex.

	All (n= 4493)	**Male (n= 2251)**	**Female (n= 2242)**
Age (years) [n_{miss}=0] *	59.6 ± 7.8	60.0 ± 7.8	59.6 ± 7.8
45-54 †	1392 (31.0%)	696 (30.9%)	696 (31.0%)
55-64 †	1772 (39.4%)	888 (39.4%)	884 (39.4%)
65-74 †	1329 (29.6%)	667 (29.6%)	662 (29.5%)
Body Mass Index (kg/m^2) [n_{miss}=0] *	27.9 ± 4.6	28.2 ± 4.0	27.7 ± 5.2
Obesity (BMI ≥ 30) [n_{miss}=0] †	1196 (26.6%)	580 (25.8%)	616 (27.5%)
Number of BMI risk alleles [n_{miss}=0] *	91.3 ± 6.2	91.0 ± 6.3	91.3 ± 6.2
Education (years) [n_{miss}=11]†			
≤10	512 (11.4%)	116 (5.2%)	396 (17.7%)
11-13	2486 (55.5%)	1065 (47.5%)	1421 (63.4%)
14-17	1005 (22.4%)	758 (33.8%)	247 (11.0%)
≥18	479 (10.7%)	303 (13.5%)	176 (7.9%)
Income (Euro/month) [n_{miss}=279] ‡	1449 (1108-1875)	1520 (1107-2072)	1313.8 (937-1874)
Lowest Quartile †	1093 (25.9%)	572 (26.5%)	521 (25.4%)
Second Quartile †	1049 (24.9%)	535 (24.8%)	514 (25.0%)
Third Quartile †	1125 (26.7%)	524 (24.2%)	601 (29.3%)
Highest Quartile †	947 (22.5%)	530 (24.5%)	417 (20.3%)
No physical activity [n_{miss}=0] †	2162 (48.1%)	1143 (50.8%)	1019 (45.4%)
Smoking status [n_{miss}=5] †			
Never	1835 (41.5%)	615 (27.8%)	1220 (55.2%)
Former + Current	2582 (58.5%)	1593 (72.2%)	989 (44.8%)
Alcohol consumption (g/week) [n_{miss}=109] ‡	13.9 (0.0; 63.7)	46.3 (6.9; 119.8)	0.9 (0.0; 15.6)

*****mean ± standard deviation (sd), † number (%), ‡ median (first quartile; third quartile), [n_{miss}= number of participants with missing values]

The mean age of the analysis population was 59.6 ± 7.8 years. The age distribution was similar in both, male and female (60.0 ± 7.8 vs 59.6 ± 7.8). Mean BMI was 27.9 ± 4.6; men showed a slightly higher BMI than women (28.2 ± 4.0 vs. 27.7 ± 5.2). Gender differences were seen regarding indicators of SES: Men reported a higher monthly household income and more men belonged to the highest education groups compared to women. Age and sex were negatively correlated with SES within the study population. Older women reported to be less educated compared to younger women of the HNR study sample. Of the analysis population 48% stated to be physically inactive, with men (50.8%) being more inactive than women (45.4%). More women (55.2%) reported to have never smoked tobacco compared to men (27.8%), while more former smoker were among men (46.4%) than women (23.1%). Current smoker were almost distributed evenly between genders, with slightly more men. A great gender difference was seen within alcohol consumption: Men declared a much higher median consumption of alcohol per week than women. In this sample, the number of genetic risk alleles ranged from 69 to 117 alleles with a mean of 91.3 ± 6.2 in the whole study population. The mean number of BMI-associated risk alleles showed no differences between men (91.3 ± 6.3) and women (91.0 ± 6.2). The genetic risk score for BMI was approximately normally distributed (Figure 9).

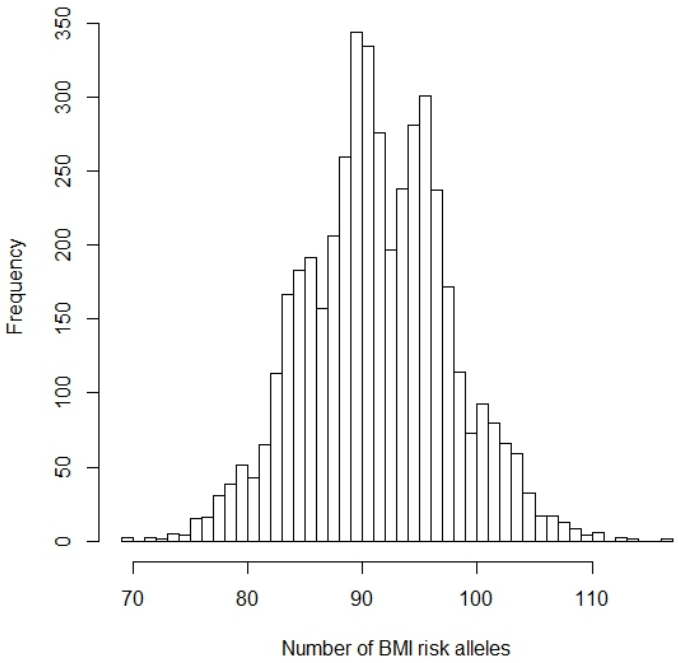

Figure 9 Distribution of BMI-associated risk alleles in the study population.

Table s-1 shows the characteristics of the study population stratified by education groups and income quartiles in which gaps between the different strata of the SES become clear. A social gradient was seen for most of the variables included in the analyses: people with a lower SES showed a higher BMI, were less physically active and were more likely to be current smoker than people with a higher SES. Alcohol consumption was highest in groups of a high SES.

The social gradient for BMI can also be observed in Table 3 showing the median BMI values for different age, education and income groups, stratified by sex and for the whole study population. Mean BMI values decreased with increasing SES and increased with age.
In contrast to stratified results of the mean BMI values, no trends were found across different age, education and income groups for the number of BMI-associated risk alleles, which are displayed in Table s-2 of the supplement. No clear pattern for the distribution of risk alleles can be distinguished across the different groups.

Table 3 Mean ± standard deviation of BMI for different age, education and income groups, stratified by sex and for the whole study population.

	All	**Male**	**Female**
Age (years)			
45-54	27.3 ± 4.8	27.8 ± 3.9	26.9 ± 5.5
55-64	27.8 ± 4.5	28.2 ± 3.9	27.4 ± 5.0
65-75	28.7 ± 4.5	28.6 ± 4.0	28.8 ± 5.0
Education (years)			
≤10	29.1 ± 5.4	28.8 ± 4.7	29.2 ± 5.6
11-13	28.0 ± 4.6	28.4 ± 3.9	27.7 ± 5.1
14-17	27.9 ± 4.3	28.3 ± 4.0	26.6 ± 5.0
≥18	26.3 ± 4.0	26.9 ± 3.5	25.3 ± 4.6
Income (Euro/month)			
Lowest Quartile	28.6 ± 4.7	28.6 ± 3.9	28.5 ± 5.4
Second Quartile	27.9 ± 4.6	28.2 ± 3.9	27.7 ± 5.1
Third Quartile	28.0 ± 4.8	28.0 ± 4.1	27.9 ± 5.3
Highest Quartile	27.2 ± 4.2	27.9 ± 3.8	26.3 ± 4.6

4.2 Association analyses

4.2.1 Marginal effects

Results of linear regression analyses of the association between income (per 1000€/ month) and education (per year of formal education) on BMI (model 1) are shown in Table 4. As expected, inequalities in health were found among the study population regarding BMI across both SES indicators. A decrease of BMI with increasing household income and years of education was observed in both sexes, with women showing the strongest effects. In females, BMI decreased by 0.89 kg/m² per additional 1000 Euro per month (95% CI: -1.22; -0.57; $p = 9.3*10^{-8}$) while BMI only decreased by 0.31 kg/m² per additional 1000 Euro per month (95% CI: -0.55; -0.08; p= 0.01) in males. Moreover, female BMI decreased by 0.37 kg/m² per additional year of formal education (95% CI: -0.47; -0.27; $p = 6.8*10^{-13}$). Compared to that, male BMI decreased by 0.14 km/m² per additional year of formal education (95% CI:-0.21; -0.07; p<0.01) (Table s-3).

Table 4 Sex- and age- adjusted effects and corresponding 95% confidence intervals (95% CI) for the association of income (per 100€/month) and education (per year) as indicators of socioeconomic status (SES) on body mass index (BMI) in linear regression models.

Model 1: BMI ~ SES + age + sex			
	n	**β (95%-CI)**	***p***
Income (1000€/month)			
Intercept	4214	25.54 (24.38; 26.71)	$<2.0*10^{-16}$
Age		0.06 (0.04; 0.08)	$2.5*10^{-11}$
Sex		-0.60 (-0.87; -0.32)	$2.8*10^{-5}$
Income		-0.59 (-0.79; -0.40)	$4.4*10^{-9}$
Education (years)			
Intercept	4482	28.68 (27.18; 30.18)	$<2.0*10^{-16}$
Age		0.05 (0.04; 0.07)	$1.1*10^{-10}$
Sex		-0.91 (-1.19; -0.63)	$3.4*10^{-10}$
Education		-0.25 (-0.31; -0.19)	$<2.0*10^{-16}$

Beta estimates and corresponding 95% confidence intervals of linear regression models for the association between the genetic risk score and BMI (model 2) are displayed in Table 5. As

expected, the genetic risk score was positively associated with BMI. An increase of one additional risk allele was associated with an increase of 0.1 kg/m² BMI in the study population (β_{GRS}= 0.10 [95% CI: 0.07; 0.12; p <2*10^{-16}]). The genetic effect was stronger in women (β_{GRS}= 0.15 [95% CI: 0.11; 0.18]; p <2*10^{-16}) than in men (β_{GRS}= 0.04 [95% CI: 0.02; 0.07]; p= 8.2*10^{-4}) (Table s-4).

Table 5 Sex- and age- adjusted effects and corresponding 95% confidence intervals (95% CI) for the association of a BMI-associated genetic risk score (GRS) on body mass index (BMI) (Model 2) in a linear regression model.

Model 2 BMI ~ GRS + age +sex			
	n	**β (95%-CI)**	***p***
Intercept	4493	15.30 (13.07; 17.53)	<2.0*10^{-16}
Age		0.07 (0.05; 0.09)	3.1*10^{-15}
Sex		-0.53 (-0.80; -0.26)	0.0001
GRS		0.10 (0.07; 0.12)	<2.0*10^{-16}

Association analyses including main effects of SES- related health behaviors on BMI are displayed in Table s-5, models 3-5. No physical activity resulted in an approximately one unit higher BMI, adjusted for SES, age and sex. Current smoking and alcohol consumption, however, showed a negative effect on BMI.

SES stratified analyses showed that the genetic effect was stronger among groups with lower SES following an inverse gradient, indicating a decreasing genetic effect with increasing SES. Participants with less than 10 years of educational training showed the strongest genetic effect (ß=0.24 [95% CI: 0.16; 0.31]; p= 3.4*10^{-10}). The genetic effect almost disappeared in the group of highest educational attainment (≥ 18 years) (ß= 0.03 [95% CI: -0.02; -0.09]; p= 0.21) (figure 11). In addition, never and current smokers showed stronger genetic effects than former smokers. Physical inactivity showed a higher genetic effect. Stratified analyses including quartiles of alcohol consumption revealed that the genetic effect followed an inverse gradient, indicating a decreasing genetic effect with increasing alcohol consumption (figure 12).

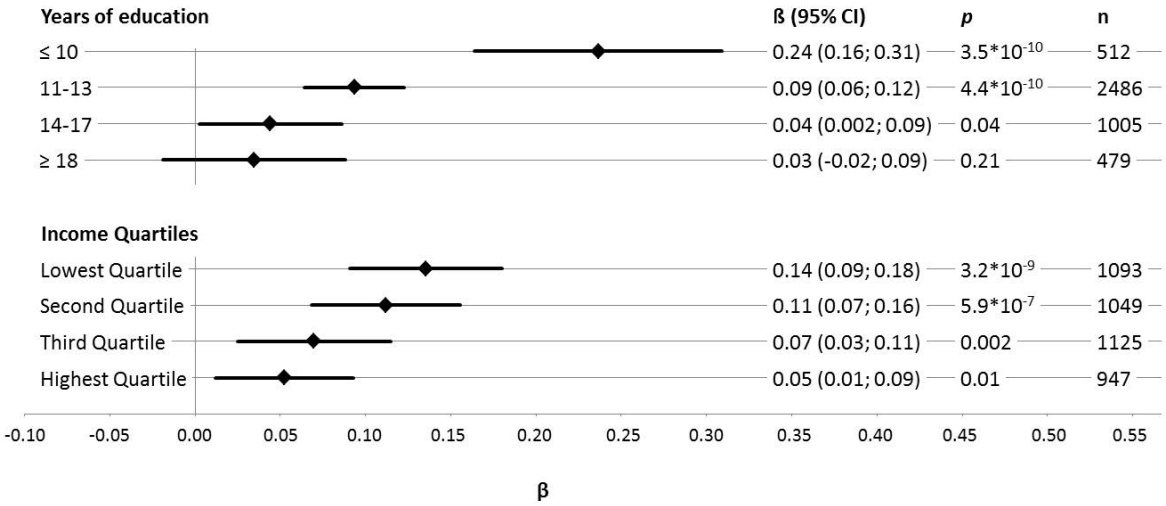

Figure 10 Sex- and age-adjusted effects and corresponding 95% confidence interval (95% CI) of the genetic effect on body mass index (BMI), stratified by education groups (years) and income quartiles in linear regression models.

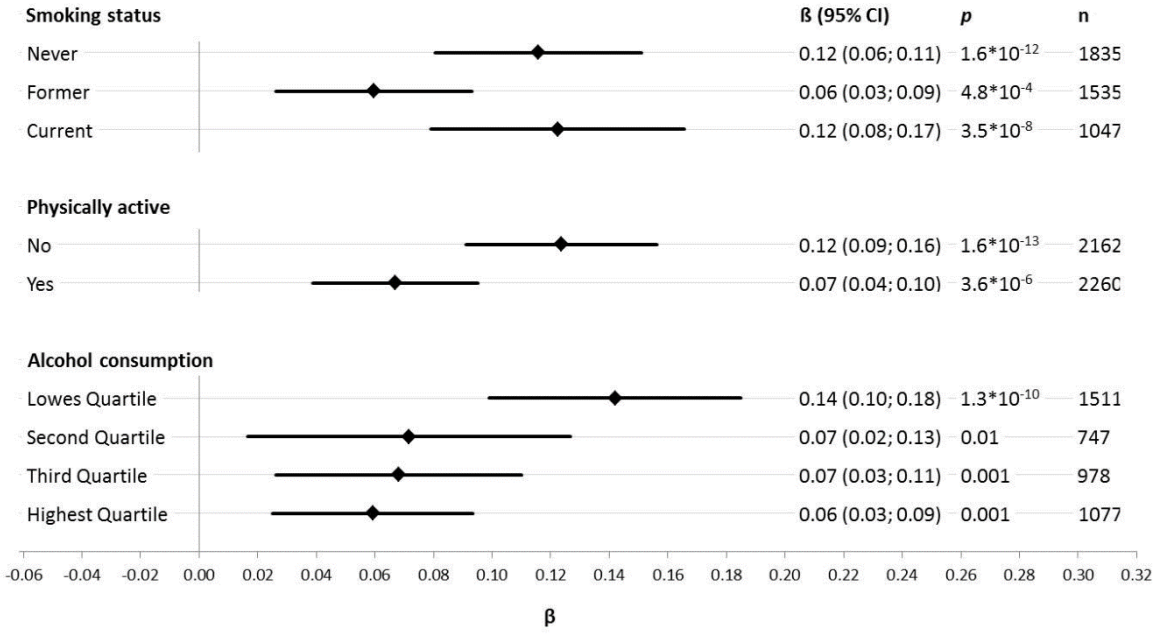

Figure 11 Sex- and age-adjusted effects and corresponding 95% confidence interval (95% CI) of the genetic effect on body mass index (BMI), stratified by smoking status, physical activity and quartiles of alcohol consumption in linear regression models.

Table 6 shows effect size estimates for the association of both SES indicators on BMI, stratified by tertiles of the GRS. Effect size estimates also displayed a clear pattern showing strongest genetic effects in groups of a high GRS.

Table 6 Sex- and age-adjusted effects and corresponding 95% confidence intervals (95% CI) of tertiles of the genetic risk score (GRS) on body mass index (BMI) in linear regression models, separately for income and education.

	n	$ß_{GRS}$ (95% CI)	*p*
Income (per 1000€)			
Low GRS	1402	-0.28 (-0.59; 0.03)	0.08
Middle GRS	1422	-0.68 (-1.02; -0.34)	$9.4*10^{-5}$
High GRS	1390	-0.83 (-1.20; -0.47)	$9.5*10^{-6}$
Education (per year)			
Low GRS	1492	-0.11 (-0.20; -0.01)	0.02
Middle GRS	1520	-0.30 (-0.40; -0.19)	$1.9*10^{-8}$
High GRS	1470	-0.34 (-0.45; -0.23)	$2.5*10^{-9}$

Participants with less than 10 years of educational training and the highest GRS tertile showed strongest genetic effects (ß= 4.54 [95% CI: 3.57; 5.51]; $p<2.0*10^{-16}$) compared to the reference group of participants with the highest educational training of 18 or more years and the lowest GRS tertile (Table 7). Effect size estimates for joint effects showed trends within and between education groups: the lower the GRS and the higher the years of educational training, the lower the effect on BMI. An exception was seen in the group of 14-17 years of education in which the trend was not as clear: participants with a low GRS showed a slightly higher joint effect (ß= 1.39 [95% CI: 0.56; 2.22]; p<0.01) than those with a middle GRS (ß= 1.10 [95% CI: 0.26; 1.93]; p=0.01). Results for the joint effect of income and GRS on BMI, however, did not show a clear pattern.

Table 7 Sex- and age-adjusted effects and corresponding 95% confidence intervals (95 % CI) on body mass index (BMI) in linear regression models of the joint effects of tertiles of a BMI-associated genetic risk score (GRS_{BMI}) and socioeconomic position indicators, calculated separately for income quartiles and education categories, with the group of having a low genetic risk score and the highest socioeconomic position as reference.

	n	β (95% CI)	*p*
Education			
≤ 10 years			
High GRS	175	4.54 (3.57; 5.51)	$<2.0*10^{-16}$
Middle GRS	170	2.72 (1.74; 3.69)	$4.6*10^{-8}$
Low GRS	167	1.62 (0.64; 2.59)	0.001
11-13 years			
High GRS	827	2.68 (1.93; 3.43)	$2.2*10^{-12}$
Middle GRS	849	1.80 (1.06; 2.55)	$2.2*10^{-6}$
Low GRS	810	1.18 (0.43; 1.93)	0.002
14-17 years			
High GRS	333	1.99 (1.15; 2.82)	$3.2*10^{-6}$
Middle GRS	329	1.10 (0.26; 1.93)	0.01
Low GRS	343	1.39 (0.56; 2.22)	0.001
≥ 18 years			
High GRS	135	0.76 (-0.26; 1.78)	0.14
Middle GRS	172	0.02 (-0.93; 0.98)	0.96
Low GRS	172	*Reference*	-
Income			
Lowest Quartile			
High GRS	295	0.19 (-0.51; 0.89)	0.59
Middle GRS	320	-0.70 (-1.38; -0.02)	0.05
Low GRS	332	-0.65 (-1.33; 0.03)	0.06
Second Quartile			
High GRS	404	0.98 (0.33; 1.62)	0.003
Middle GRS	366	0.31 (-0.35; 0.97)	0.35
Low GRS	355	-0.37 (-1.04; 0.29)	0.27
Third Quartile			
High GRS	340	1.24 (0.57; 1.91)	0.0003
Middle GRS	355	-0.08 (-0.75; 0.58)	0.81
Low GRS	354	-0.30 (-0.96; 0.37)	0.38
Highest Quartile			
High GRS	351	1.77 (1.10; 2.44)	$2.0*10^{-7}$
Middle GRS	381	0.69 (0.03; 1.34)	0.04
Low GRS	361	*Reference*	-

4.2.2 Interaction analyses

Regression analyses, adjusted for age and sex, including GRS and SES main effects and respective GRSxSES interaction terms, separately both SES indicators, gave indication for interaction. Negative beta estimates were seen for income ($ß_{GRSxIncome}$= -0.05 [95% CI: -0.08; -0.02; p<0.01] per 1000€/month increase and additional risk allele) (Table 8, model 6) and for education ($ß_{GRSxEducation}$= -0.02 [95% CI: -0.03; -0.01]; p= $1.27*10^{-5}$, per year of education and additional risk allele) (Table 9, model 6).
Sex-stratified analyses showed similar effect size estimates for GRSxSES interaction; the GRSxIncome interaction, however, was not statistically significant for both sexes (Table s-6 for income and Table s-7 for education, model 6).

Effect size estimates of the GRSxSES interaction did not substantially change for both SES indicators after including additional SES-related health behaviors (physical inactivity, smoking and alcohol consumption) and their interaction terms with the GRS to the model (models 7-9) (Table 8 for income and table 9 for education). An indication for GRS by physical activity interaction was found in models controlled for income ($ß_{GRSxPA}$= 0.06 [95% CI: -0.01; 0.10]; p=0.01) (Table 8, model 7) and for education ($ß_{GRSxPA}$= 0.05 [95% CI: 0.002; 0.09]; p= 0.04) (Table 9, model 7). Indication for interaction was observed neither for GRSxS, nor for GRSxAlc. Sex-stratified analyses are displayed in supplementary Table s-6 for income and Table s-7 for education, showing overall slightly stronger effect size estimates in women than in men. Likewise, the effect sizes of the GRSxSES interactions did not change in sex-stratified analyses when additionally including interaction terms of GRS by indicators of SES-related health behavior to model 6. Further, positive interactions were only found in women for the GRS by physical activity interaction for both, income ($ß_{GRSxPA}$= 0.09 [95% CI: 0.02; 0.16]; p= 0.01) and education ($ß_{GRSxPA}$= 0.07 [95% CI: 0.01; 0.14]; p= 0.04).

In addition, interaction with income was further found for physical activity, smoking and alcohol consumption (Table 8), while smoking and alcohol consumption interacted also with education (Table 9). Sex-stratified analyses showed an income x PA ($ß_{IncomexPA}$= 0.72 [95% CI: 0.25; 1.19]; p< 0.01) and an income x S ($ß_{IncomexS}$= 0.56 [95% CI: 0.04; 1.08]; p= 0.04) interaction effect in men, which was smaller than the found income by smoking interaction effect in women ($ß_{IncomexS}$= 0.85 [95% CI: 0.09; 1.61]; p= 0.03) (Table s-6). An interaction between education and indicators of health behaviors was only found for smoking in women ($ß_{EducationxS}$= 0.31 [95% CI: 0.07; 0.55]; p= 0.01) (Table s-7). Excluding income as an SES indicator from models 7-9 resulted in no changes

in interaction effect size estimates. Nevertheless, an exclusion of education from the model resulted in slightly stronger effect size estimates of the GRSxPA and the GRSxA interaction effect size estimates (comparison of Table 8 and Table 9, models 7-9 with table 10, models 10-12).

Table 8 Sex- and age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) in linear regression models including main effects and interaction terms of a BMI-associated genetic risk score (GRS), 1000€ income/month as an indicator of socioeconomic status (SES) and SEE-related health behaviors (no physical activity [PA], current smoking [S], alcohol consumption [Alc; per 100g/week]).

	Model 6 (n= 4214) BMI ~ SES + age + sex + GRS + GRS*SES		**Model 7** (n=4147) BMI ~ SES + age + sex + GRS + PA + GRS*SES + GRS*PA + SES*PA		**Model 8** (n= 4147) BMI ~ SES + age + sex + GRS + S + GRS*SES + GRS*S + SES*S		**Model 9** (n= 4057) BMI ~ SES + age + sex + GRS + Alc + GRS*SES + GRS*Alc + SES*Alc	
	β (95%-CI)	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***
Intercept	10.15 (5.17; 15.10)	$6.5*10^{-5}$	13.90 (8.30; 19.50)	$1.2*10^{-6}$	12.84 (7.67; 18.01)	$1.1*10^{-6}$	9.96 (4.92; 15.00)	0.0001
Age	0.06 (0.04; 0.08)	$4.5*10^{-12}$	0.06 (0.04; 0.08)	$1.8*10^{-10}$	0.05 (0.03; 0.06)	$5.6*10^{-7}$	0.06 (0.05; 0.08)	$2.5*10^{-5}$
Sex	-0.59 (-0.86; -0.31)	$3.0*10^{-5}$	-0.50 (-0.78; -0.22)	0.00042	-0.62 (-0.90; -0.34)	$1.3*10^{-5}$	-0.64 (-0.93; -0.34)	$2.3*10^{-12}$
Income	3.08 (-1.42; 7.58)	<0.01	2.84 (0.05; 5.63)	0.05	3.22 (0.46; 5.99)	0.02	3.08 (0.29; 5.87)	0.03
GRS	0.17 (0.11; 0.22)	$5.8*10^{-10}$	0.13 (0.07; 0.19)	$3.0*10^{-5}$	0.15 (0.10; 0.21)	$3.4*10^{-8}$	0.17 (0.12; 0.23)	$3.6*10^{-10}$
No physical activity	-	-	-5.24 (-9.33; -1.15)	0.01	-	-	-	-
Current smoking	-	-	-	-	-5.37 (-10.20; -0.54)	0.03	-	-
Alcohol consumption	-	-	-	-	-	-	1.17 (-0.60; 2.93)	0.20
GRS x Income	-0.05 (-0.08; -0.02)	<0.01	-0.04 (-0.07; -0.01)	0.01	-0.04 (-0.07; -0.01)	0.004	-0.04 (-0.07; -0.01)	0.01
GRS x PA	-	-	0.06 (0.01; 0.10)	0.01	-	-	-	-
GRS x S	-	-	-	-	0.03 (-0.02; 0.09)	0.19	-	-
GRS x Alc	-	-	-	-	-	-	-0.02 (-0.04; 0.002)	0.07
Income x PA	-	-	0.59 (0.20; 0.98)	0.003	-	-	-	-
Income x S	-	-	-	-	0.76 (0.32; 1.21)	0.001	-	-
Income x Alc	-	-	-	-	-	-	0.23 (0.07; 0.40)	0.01

Table 9 Sex- and age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) in linear regression models including main effects and interaction terms of a BMI-associated genetic risk score (GRS), years of education as an indicator of socioeconomic status (SES) and SEE-related health behaviors (no physical activity [PA], current smoking [S], alcohol consumption [Alc; per 100g/week]).

	Model 6 (n= 4482) BMI ~ SES + age + sex + GRS + GRS*SES		**Model 7** (n= 4411) BMI ~ SES + age + sex + GRS + PA + GRS*SES + GRS*PA + SES*PA		**Model 8** (n= 4411) BMI ~ SES + age + sex + GRS + S + GRS*SES + GRS*S + SES*S		**Model 9** (n= 4305) BMI ~ SES + age + sex + GRS + Alc + GRS*SES + GRS*Alc + SES*Alc	
	β (95%-CI)	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***
Intercept	-4.93 (-16.35; 6.49)	0.4	-0.22 (-12.19; 11.76)	0.97	-1.69 (-13.21; 9.84)	0.77	-3.09 (-14.70; 8.51)	0.60
Age	0.05 (0.04; 0.07)	$5.9*10^{-10}$	0.05 (0.03; 0.07)	$3.0*10^{-8}$	0.04 (0.02; 0.06)	$3.8*10^{-5}$	0.06 (0.04; 0.07)	$3.8*10^{-10}$
Sex	-0.91 (-1.19; -0.63)	$1.8*10^{-10}$	-0.81 (-1.09; -0.52)	$5.9*10^{-9}$	-1.00 (-1.28; -0.71)	$6.5*10^{-12}$	-0.96 (-1.26; -0.66)	$3.6*10^{-10}$
Education	1.52 (0.73; 2.32)	<0.001	1.32 (0.51; 2.13)	0.001	1.44 (0.64; 2.24)	$4.2*10^{-4}$	1.34 (0.52; 2.16)	0.001
GRS	0.37 (0.24; 0.49)	$7.9*10^{-9}$	0.31 (0.18; 0.44)	$2.7*10^{-6}$	0.36 (0.23; 0.48)	$2.5*10^{-8}$	0.35 (0.23, 0.48)	$4.5*10^{-8}$
Physical activity	-	-	-4.16 (-8.46; 0.13)	0.06	-	-	-	-
Current smoking	-	-	-	-	-7.18 (-12.25; -2.12)	0.01	-	-
Alcohol consumption	-	-	-	-	-	-	0.14 (-1.77; 2.04)	0.89
GRS x Education	-0.02 (-0.03; -0.01)	$1.27*10^{-5}$	-0.02 (-0.03; -0.01)	$1.5*10^{-4}$	-0.02 (-0.03; -0.01)	$1.6*10^{-5}$	-0.02 (-0.03; 0.01)	$8.9*10^{-5}$
GRS x PA	-	-	0.05 (0.002; 0.09)	0.04	-	-	-	-
GRS x S	-	-	-	-	0.03 (-0.02; 0.08)	0.26	-	-
GRS x Alc	-	-	-	-	-	-	-0.01 (-0.03; 0.01)	0.20
Education x PA			0.06 (-0.06; 0.17)	0.32	-	-	-	-
Education x S			-	-	0.25 (0.11; 0.39)	$4.0*10^{-4}$	-	-
Education x Alc			-	-	-	-	0.06 (0.01; 0.12)	0.02

Table 10 Sex- and age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) in linear regression models including main effects and respective interaction terms of a BMI-associated genetic risk score (GRS) and socioeconomic status-related health behaviors (no physical inactivity [PA], current smoking [S], alcohol consumption [Alc; per 100g/week]).

	Model 10 (n= 4422) BMI ~ age + sex + GRS + PA + GRS*PA		**Model 11** (n= 4417) BMI ~ age + sex + GRS + S + GRS*S		**Model 12** (n= 4313) BMI ~ age + sex + GRS + Alc + GRS*Alc	
	β (95%-CI)	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***
Intercept	17.68 (14.75; 20.60)	$<2.0*10^{-16}$	16.93 (14.42; 19.44)	$<2.0*10^{-16}$	14.14 (11.62; 16.66)	$<2.0*10^{-16}$
Age	0.06 (0.05; 0.08)	$4.0*10^{-13}$	0.06 (0.04; 0.07)	5.2*10-10	0.07 (0.05; 0.09)	1.8*10-15
Sex	-0.46 (-0.73; -0.19)	0.001	-0.53 (-0.80; -0.26)	0.0001	-0.57 (-0.86; -0.28)	0.0001
GRS	0.07 (0.04; 0.10)	$7.0*10^{-6}$	0.09 (0.06; 0.11)	1.6*10-12	0.11 (0.08; 0.13)	$<2.0*10^{-16}$
No physical activity	-4.17 (-8.11; -0.24)	0.04	-	-	-	-
Current smoking	-	-	-3.51 (-8.19; 1.17)	0.14	-	-
Alcohol consumption	-	-	-	-	0.71 (-0.02; 3.43)	0.05
GRS x PA	0.06 (0.01; 0.10)	0.01	-	-	-	-
GRS x S	-	-	0.03 (-0.02; 0.08)	0.28	-	-
GRS x Alc	-	-	-	-	-0.02 (-0.04; -0.001)	0.04

In order to follow up on the results of the GRS interaction analysis each of the 97 BMI-associated SNPs were also tested separately for interactions with both SES-indicators (Table s-12 and Table s-13) and with SES-related health behaviors physical activity (Table s-14), smoking (Table s-15) and alcohol consumption (Table s-16), adjusted for age and sex. None of the SNPs interactions were statistically significant after correcting for multiple testing using Bonferroni's method (α_{BF} = 0.05/(5*97 tests) = 0.000103). The effect size estimates for interaction were close to each other in the range of -0.17 – 0.20 for education, -0.32 – 0.38 for income, -0.75 – 0.55 for physical activity, -0.89 – 0.67 and -0.33 – 0.42 for alcohol consumption. For some single SNPs, interactions effect size estimates point in the opposite direction compared to the direction of the respective GRS interaction effect. Nevertheless, variant rs9540493 (*MIR548X2*) appeared to have the strongest negative interaction effect with income, variant rs11057405 (*CLIP1*) with education. Variants rs2176598 (*HSD17B12*) and rs6567160 (*MC4R*) were found to have the strongest positive interaction effect with physical activity. The strongest positive interaction effect was observed for variant rs6567160 (*MC4R*) with smoking, while rs7239883 (*LOC284260*) showed the strongest negative interaction with alcohol consumption (Table s-14 - Table s-16).

Comparing the twenty strongest negative SNP by education interaction effects with the twenty strongest negative SNP by income interaction effects it was seen that nine SNPs appeared among both twenty strongest interaction effects, displayed in Table 11. This Table shows further that additional overlaps were seen within each of the top twenty interaction effects with SES-related health behaviors, marked with a cross in the table. Of the SNPs that interacted with education, one additional overlap was seen for five SNPs, while three SNPs showed two overlaps. One additional overlap was noted for 5 SNPs that interacted with income, while one SNP showed an overlap with smoking and alcohol consumption. Of the nine SNPs that were among the top twenty SNPxEducation as well as the top twenty SNPxIncome interaction effects, 5 SNPs showed one additional overlap with at least one health behavior. While variant rs10132280 (*STXBP6*) was among the top twenty interaction analyses with income, education, smoking and alcohol consumption, variant rs29941 (*KCTD15*) was present among all five top twenty interaction analyses.

Table 11 Comparison of the top twenty SNPs that showed strongest interaction effects with education and interaction, and the top twenty SNP by SES-related health behavior interactions.

	Top 20 SNP with strongest interaction effect		**Interaction of SNPs with health behaviors**		
	SNP	**Locus**	**Physical activity**	**Smoking**	**Alcohol consumption**
Education	rs11057405	*CLIP1*	x		
	rs12885454	*PRKD1*	x		
	rs2035935 †	*RASA2*	x		x
	rs6804842	*RARB*			
	rs4256980	*TRIM66*	x		
	rs13107325	*SLC39A8*		x	
	rs10968576	*LINGO2*		x	x
	rs11583200	*ELAVL4*			
	rs11126666	*KCNK3*			
	rs17094222	*HIF1AN*	x	x	
	rs3888190	*ATP2A1*		x	
Education and income	rs758747	*NLRC3*		x	
	rs9540493	*MIR548X2*			
	rs2287019	*QPCTL*		x	
	rs7715256	*GALNT10*	x		
	rs1167827	*HIP1*	x		
	rs10132280	*STXBP6*		x	x
	rs29941	*KCTD15*	x	x	x
	rs10938397	*GNPDA2*			
	rs2033732	*RALYL*			x
Income	rs13078960	*CADM2*			x
	rs7243357	*GRP*	x		
	rs2176598	*HSD17B12*	x		
	rs1460676	*FIGN*			
	rs9581855 ǂ	*MTIF3*			
	rs11727676	*HHIP*		x	
	rs1808579	*C18orf8*			
	rs205262	*C6orf106*			
	rs7239883	*LOC284260*			x
	rs2650492	*SBK1*		x	x
	rs1516725	*ETVM*			

† rs2035935 as a proxy SNP for rs16851483; ǂ rs9581855 as a proxy SNP for rs12016871

X indicates that the respective loci is also among the top twenty interaction effects with SES-related health behavior(s)

5 Discussion

5.1 Main findings

The aim of this thesis was to determine whether SES differences have an influence on the effect of a BMI-associated genetic risk allele sum score on BMI in a population-based cohort. Negative interactions between genetic factors related to BMI with education and income as indicators of SES were identified, indicating that the combined effect of the GRS and SES was more than the sum of their marginal effects on BMI. This was supported by results obtained in stratified analyses in which lowest genetic effects were seen in groups of high SES. Also, comparing joint effects of all possible combinations of tertiles of the genetic risk score and SES groups showed the lowest effect on BMI in participants within the highest education group and the lowest genetic risk. After further including variables of SES-related health behavior (i.e., smoking, physical activity and alcohol consumption) as potential mediators of the found GRSxSES interaction effects, the negative GRSxSES interaction effect size estimates remained virtually unchanged, suggesting that the health behaviors included in the analysis do not explain the foung GRSxSES interaction. In addition, independent of the SES effect, indication for a positive GRSxPA interaction was found. Interaction analyses with single SNPs and SES indicators education and income revealed substantial overlap of top SNPs. Overlaps were further seen with top SNPs of SES-related health behaviors. The findings will be discussed in more detail in the following paragraphs.

5.2 Marginal effects

Results of regression analyses showed a clear association between SES and BMI: A higher net household income and more years of schooling were associated with a decrease in BMI. Age and SES are negatively correlated within HNR, older women showed to be lower educated than younger women. Thus, association analyses were adjusted for age and sex as confounder. An inverse association was also found for current smoking and alcohol consumption, while the association of alcohol and BMI was rather small. No physical activity was associated with an increase in BMI. The magnitude and direction of effect size estimates of the present results are similar to those reported in literature (Galobardes et al., 2000; Hermann et al., 2011; Plurphanswat and Rodu, 2014; Salonen et al., 2009; Young et al., 2016). Literature implies that

the exposure to risk factors is more prevalent among lower socioeconomic groups where people are less likely, e.g., to participate in regular physical activity and are more likely to eat a high-fat diet (Ball et al., 2002; House et al., 1994). Education represents both, long term influences of early life circumstances on health outcomes in later life and the influences that resources gained in adult life (such as the employment status) have on health (Galobardes et al., 2006). High levels of education go along with a higher occupational status and thus more income, better working and housing conditions. The effect of education on BMI is likely to be determined by the fact that higher educated people may be more engaged in health-promoting behavior and lifestyles, e.g., being more physically active. They might also have a greater perception of health risks, which could lead to a lower BMI. Further, higher educated people may have a better ability to integrate healthy behaviors into a coherent lifestyle, showing a higher sense of control over their weight (Mirowsky and Ross, 1998). The income of a person influences material circumstances which also have an effect on the (health) behavior of an individual: It allows the access to material goods and services that might be required to maintain a healthy weight and foster their social standing, such as the consumption of foods with reduced saturated fats or the membership in fitness centers resulting in regular physical exercise (Galobardes et al., 2006). In sex-stratified analyses, both SES indicators were inversely associated with BMI, however, while pointing in the same direction effect size estimates in women where slightly stronger than in men. This corresponds with results of previous studies (Molarius et al., 2000; Thurston et al., 2005). It has been stated that evidence for an inverse relationship between education (Lahmann et al., 2000) and income with obesity exist among women in developed countries, whereas this relationship is less consistent among men (Ball et al., 2002; Salonen et al., 2009; Wardle et al., 2002). An explanation might be that women experience stronger social pressure to retain a lower body weight due to greater social stigma and discrimination, especially within higher socioeconomic groups (Thurston et al., 2005).

Studies on the association of alcohol intake on body weight are rather inconclusive (Traversy and Chaput, 2015). People with a higher SES tend to consume more alcohol, which was also shown among participants of the HNR study, and literature suggests that people with low SES are more negatively affected by alcohol-related consequences (Collins, 2016). Moreover, it has been reported that the consumption of alcohol and smoking is related, i.e., people who drink higher amounts of alcohol usually smoke and vice versa (Leon et al., 2007). Although the mechanisms of current smoking on BMI are complex, one explanation for the inverse relationship found in the present analyses may be the nicotine intake which suppresses eating

behavior, increases energy expenditure and decreases the metabolic rate (Audrain-McGovern and Benowitz, 2011).

The results of association analyses of the genetic risk score and BMI underline the clear association of the selected SNPs with the phenotype. The effect size estimate observed for the increase of BMI per additional risk allele is consistent with the results of previous studies (Locke et al., 2015). Moreover, a gradient of the genetic effect was seen within groups of SES, where the lowest genetic effect was observed in groups of highest SES. Joint effects of all possible combinations of GRS tertiles and SES groups supported this finding. This is coherent to previous studies which have indicated that education modifies genetic and environmental influences on BMI (Amin et al., 2017; Johnson et al., 2010). Although results obtained using income as an SES indicator where not as clear compared to results using education as an SES indicator, a modification of the genetic effect was also observed within groups of higher income, suggesting an interaction between the GRS and SES.

5.3 Interaction analyses

Results of the present analyses including GRS, SES and respective interaction terms gave indication for negative interaction between a genetic risk score of 97 variants associated with BMI and SES indicators income and education. The direction of interaction effect size estimates conforms to results of earlier studies. Within a sample of the US-American Health and Retirement Study, an interaction between a BMI-associated GRSs and education, measured as self-reported years of schooling and degrees of educational attainment (less than high school, high school and college), has been observed. The direction of interaction effects was consistent with the present study, albeit estimates were statistically non-significant (Liu et al., 2015). Similarly, although also statistically non-significant, smaller genetic effects have been found within groups of higher educational attainment, measured in four categories in two different study samples (Amin et al., 2017). Recent studies have reported interactions between a BMI-associated GRS and the cumulative area-related Townsend deprivation index (TDI) used as a measure of SEP, within study samples of the UK Biobank (Rask-Andersen et al., 2017; Tyrrell et al., 2017). Interactions between the GRS and job class and level of education, measured by the ISCED, have been additionally assessed and revealed also non-significant results (Tyrrell et al., 2017). Comparable to the present study, results of an interaction between a BMI-associated GRS and household income before tax have been shown within the study of Rask-Andersen et al. in

which 131 environmental factors have been assessed in their interaction with a GRS (Rask-Andersen et al., 2017). Thus, results of previous studies and the present findings give supporting indications for the hypothesized GRSxSES interaction on BMI.

Each of the two SES indicators represents certain aspects of the SES of a person related to different health behaviours and risks and even though education and income are correlated, several causual pathways have been described: Higher educated people might have better knowledge about promoting health skills and thus a a greater control over important health determinants, such as healthy nutrition, regular physical activity. Through higher income people might experience a higher social standing, lower levels of stress due to better access to recreational facilities and healthier food (Galobardes et al., 2000; Johnson et al., 2011; Johnson and Krueger, 2005). SES might also have an effect on the genetic susceptibility to higher BMI via these pathways, including the possibility of altered gene expression by epigenetic mechanisms, e.g, changes in DNA methylation and histone modification. Previous studies have demonstrated that DNA methylation is an important mechanism involved in the regulation of gene expression and is associated with the socioeconomic status of a person (Borghol et al., 2012; McGuinness et al., 2012). Lifestyle behaviors such as diet (Sonestedt et al., 2009), physical activity and alcohol intake are known to influence DNA methylation, indicating that methylation might be a biological mechanism bridging the impact of genetic variation and environmental factors on BMI (Subramanyam et al., 2013).

However, in this thesis, GRSxSES interactions additionally adjusted for physical activity, smoking or alcohol consumption as potentially mediating factors resulted in non-substantial changes in effect size estimates of the GRSxSES interaction effect, indicating that this interaction is not mediated by such factors. Consequently, it can be suggested that other indicators besides the presently tested might have a mediating effect on the found GRSxSES interaction. A previous study that has as well found an interaction between a BMI-associated GRS and education within a Finnish study sample, also reported only a slight attenuation of the interaction effect after further adjusting for main effect of physical activity and respective interaction term (Komulainen et al., 2017). Comparable to earlier studies, indication for positive interaction between the GRS and physical activity was obtained in the present study, while no indication for a GRS_{BMI}xSmoking or GRS_{BMI}xAlcohol interaction was seen (Ahmad et al., 2013; Li et al., 2010; Rask-Andersen et al., 2017). In excluding SES indicators and GRSxSES interaction terms from the models, the GRS by health behavior interactions were corrected for possible confounding by SES, which revealed no

confounding effect of income while education seemed to confound the found GRSxPA and GRSxAlc interaction.

When interpreting results of interactions between a genetic risk allele sum score and SES, the perspective lays on the cumulative genetic risk of a person and the cumulative effect of risk factors related to social inequality. Thus, results of interaction analysis are to be interpreted rather global. Testing SNPs in their individual interaction with environmental factors may reveal single pathways that might not be detected as their single effect would be too low or masked by the interaction effect of other SNPs combined in the score. However, results of the single SNP analyses have to be interpreted with caution, as statistical power was too low to detect interaction effect size estimates of sufficient precision. When looking at the effect size estimates of the interactions between individual SNPs and both SES indicators, effect sizes were found to be in a range close to each, indicating that no single variant alone substantially triggered the observed GRS by SES interactions, which is similar to results of a previous study (Tyrrell et al., 2017). In this study, the variant of the fat-mass and obesity-associated *FTO* gene did not belong to the SNPs with strongest SES or SES-related health behavior interaction effects which is contrasting to results of previous studies (Ahmad et al., 2013; Cauchi et al., 2009; Corella et al., 2012; Foraita et al., 2015). Of twenty SNPs with the strongest SNP*x*SES interaction effects, overlaps with the twenty strongest SNP by health behavior interactions were found. The frequency of overlaps was found to be higher than expected. Even though the overall picture did not indicate that the GRSxSES interaction was mediated by underlying interactions of the GRS and SES-related health behaviors, results of interaction analyses with single SNPs revealed that the interaction with SES-related health behaviors seemed to be a relevant mediator. This could mean that the GRS*x*Education and GRS*x*Income interactions are at least partly mediated by the same genes. The fact that overlaps were also seen with health behaviors could suggest that for some SNPs the GRS*x*SES interaction is mediated by the corresponding health behavior.

5.4 Strengths and limitations

The population-based study sample and the use of two separate SES indicators in the analyses, rather than a cumulative SES indicator, are the main strength of this thesis. Also, evidence on interaction was not only based on testing interaction between the GRS and indicators of SES, but also on stratified analyses and calculations of joint effects of GRS and SES indicators. Another

advantage of the present study is that other environmental factors potentially underlying the GRSxSES interaction effect on BMI were included in the analyses.

The sample size of this study is one limitation of the present work. Large sample sizes are required for the detection of small interaction effect size estimates, especially for interaction analyses with single variants. Thus, to increase the statistical power it was chosen to use the GRS in the main analysis. In addition, other potential factors underlying the GRSxSES interaction (e.g. specific dietary factors) that have not been included in the present analysis need to be considered. Another limitation is the potential bias in the self-reported data on SES-related health behavior physical activity, alcohol consumption and smoking behavior. Last, due to the age range of HNR study participants it was not able to report on interactions between childhood/youth BMI and SES during childhood/youth.

5.5 Conclusion and further perspectives

The results of the present study provide indication for an additive interaction of BMI-associated genetic factors with education and income used as indicators of SES in a population-based cohort. From a public health viewpoint this research provides added value as it improves the understanding of disease pathology at molecular level. It further gives support to claims of previous studies that vulnerable groups, e.g., people with a low SES, are in need of more support as they experience greater health risks. Present results underline the fact that prevention strategies and intervention programs could benefit from a deeper understanding of underlying interactions of genetic predisposition and socioeconomic factors to establish focus on groups of individuals of high risk. Adding to the knowledge of previous studies, results of this paper showed that a person's SES seems to modify the expression of BMI-associated genetic variants, irrespective of a person's physical activity, smoking behavior or alcohol consumption. The observed GRSxSES interaction has thus to be explained by other underlying interaction effects than those integrated into the present analyses. To fully understand the complex relation between genetic variants and the environment resulting in a higher weight, further research must consider other factors that might modify the effect of BMI variants on high weight, e.g., dietary patterns or levels of stress. Also, analyses should be extended to other examples of complex conditions diseases as for instance diabetes or coronary artery diseases.

6 Summary

Past research has shown that obesity is influenced by both, environmental factors and genetic variants. Twin studies suggested that the impact of some genetic variants depends on certain environmental exposures such as the socioeconomic status (SES), indicating gene by SES interaction. Empirical studies examining GxSES on body mass index (BMI), used as a surrogate marker for the risk of obesity, incorporating genome-wide molecular genetic information are, however, limited and do not include underlying risk factors potentially responsible for the interaction effects detected. This thesis aimed to investigate whether a sum score (GRS) of 97 BMI-associated variants interacts with income and education, used as contextual markers of socially differing environmental conditions. Within the study population inequalities in health were seen for both SES indicators on BMI and an increase of BMI per additional risk allele was observed. Negative GRSxSES interaction was found, showing stronger genetic effects in groups of lower SES. To explore whether these interactions were due to underlying interactions with SES-related health behaviours, smoking, physical activity and alcohol consumption were included into analyses, not affecting the magnitude and direction of the observed GRSxSES interaction. Independent of the SES effect, a positive GRSxPA interaction was found. Further, income did not have a confounding effect on the GRSxPA, GRSxS and GRSxAlc interactions, while GRSxPA and GRSxAlc interactions might be party confounded by education. Sex-stratified analyses showed overall slightly stronger effect size estimates in women than in men. Interactions between individual SNPs and both SES indicators revealed effect size estimates close to each other, indicating that no single variant alone substantially triggered the observed GRSxSES interactions. Also, overlaps among the highest SNPxSES interaction effects were found to be more frequent than expected, suggesting that the GRS*x*Education and GRS*x*Income interactions are at least partly mediated by the same genes. The fact that overlaps were also seen with health behaviors could suggest that for some individual SNPs the GRS*x*SES interaction is mediated by health behaviors. Present results support the hypothesis that individuals in higher SES groups are enabled to reduce their genetic susceptibility to disease through better material, behavioral and psychosocial factors. Although the found GRSxSES interaction seems not to be explained by physical activity, smoking or alcohol consumption, further research must consider other factors that might modify the effect, e.g. dietary patterns or levels of stress. Further analyses could also be extended by other examples of complex conditions such as diabetes or coronary artery diseases.

7 References

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8 Supplementary material

8.1 Tables

Table s- 1 Characteristics of the study population stratified by income quartiles and education groups.

Education (years)		**≤ 10**	**11-13**	**14-17**	**≥ 18**
N (%)		512 (11.4%)	2486 (55.5%)	1005 (22.4%)	479 (10.7%)
Age (years)		63.3 ± 7.5	59.6 ± 7.7	59.3 ± 7.7	56.4 ± 7.2
Number of BMI risk alleles (GRS)		91.5 ± 6.2	91.3 ± 6.2	91.3 ± 6.3	90.8 ± 6.7
Body Mass Index (kg/m^2)		28.6 ± 4.7	27.9 ± 4.6	28.0 ± 4.8	27.2 ± 4.2
Income (€/month)		1108.0 (861.8- 1308.0)	1278.0 (975.5- 1662.0)	1743.0 (1278.0- 2216.0)	2216.0 (1743.0- 2897.0)
Current smoker		101 (20.0%)	642 (26.2%)	989 (22.0%)	84 (17.8%)
No physical activity		314 (62.3%)	1259 (51.5%)	436 (44.1%)	147 (31.1%)
Alcohol consumption (g/week)		0.0 (0.0; 14.6)	8.1 (0.0; 55.6)	32.2 (3.7; 111.2)	37.0 (2.8; 107.0)
Income (Euro/month)		**Lowest Quartile**	**Second Quartile**	**Third Quartile**	**Highest Quartile**
N (%)		1093 (25.9%)	1049 (24.9%)	1125 (26.7%)	947 (22.50%)
Age (years)		62.0 ± 7.6	59.7 ± 8.1	59.4 ± 7.9	57.8 ± 7.2
Body Mass Index (kg/m^2)		28.6 ± 4.7	28.0 ± 4.6	28.0 ± 4.8	27.2 ± 4.2
Number of BMI risk alleles (GRS)		91.3 ± 6.2	91.3 ± 6.2	91.5 ± 6.2	91.1 ± 6.5
Education (years)	≤10	225 (20.6%)	149 (14.2%)	85 (7.6%)	20 (2.1%)
	11-13	700 (64.1%)	635 (60.5%)	647 (57.5%)	326 (34.4%)
	14-17	147 (13.5%)	213 (20.3%)	293 (26.0%)	316 (33.4%)
	≥18	20 (1.8%)	52 (5.0%)	100 (8.9%)	285 (30.1%)
Current smoker		286 (26.7%)	238 (23.0%)	237 (21.3%)	213 (22.8%)
No physical activity		640 (56.5%)	526 (50.8%)	496 (44.7%)	366 (39.2%)
Alcohol consumption (g/week)		6.9 (0.0; 55.6)	11.12 (0.00; 59.8)	11.4 (0.0; 66.1)	27.8 (0.0; 97.9)

Values are expressed as mean ± standard deviation, median (first quartile; third quartile), or proportion (%).

Table s- 2 BMI-associated risk alleles (mean ± standard deviation) for different age, education and income groups for the whole study population and stratified by sex.

	Male	Female	All
Age (in years)			
45-54	91.5 ± 6.4	91.2 ± 6.4	91.3 ± 6.4
55-64	91.1 ± 6.4	91.1 ± 6.0	91.1 ± 6.2
65-75	91.3 ± 6.0	91.5 ± 6.3	91.4 ± 6.2
Education (in years)			
≤10	90.8 ± 6.0	91.7 ± 6.3	91.5 ± 6.2
11-13	91.4 ± 6.2	91.3 ± 6.1	91.3 ± 6.2
14-17	91.4 ± 6.2	91.3 ± 6.4	91.3 ± 6.3
≥18	91.2 ± 6.8	90.0 ± 6.2	90.8 ± 6.6
Income			
Lowest Quartile	91.3 ± 6.0	91.3 ± 6.3	91.3 ± 6.2
Second Quartile	91.4 ± 6.2	91.2 ± 6.3	91.3 ± 6.2
Third Quartile	91.5 ± 6.4	91.4 ± 6.1	91.5 ± 6.2
Highest Quartile	91.2 ± 6.4	91.1 ± 6.6	91.1 ± 6.5
Physical activity			
Yes	91.5 ± 6.4	91.1 ± 6.3	91.3 ± 6.4
No	91.1 ± 6.1	91.5 ± 6.1	91.3 ± 6.1
Smoking status			
Never	91.2 ± 6.4	91.0 ± 6.2	91.1 ± 6.2
Former	91.3 ± 6.3	91.5 ± 6.3	91.4 ± 6.3
Current	91.4 ± 6.1	91.6 ± 6.2	91.5 ± 6.2
Alcohol consumption			
Lowest Quartile	91.5 ± 5.9	91.4 ± 6.2	91.5 ± 6.1
Second Quartile	90.7 ± 5.9	91.6 ± 6.4	91.3 ± 6.0
Third Quartile	91.6 ± 5.9	90.5 ± 6.0	91.2 ± 6.0
Highest Quartile	91.1 ± 6.7	90.8 ± 6.4	91.0 ± 6.4

Table s- 3 Age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) of the association of income (per 100€/month) and education (per year) as indicators of socioeconomic status (SES) in sex-stratified linear regression models.

Model 1 BMI ~ SES + age				
		n	**β (95% CI)**	***p***
Male	**Income (1000€/month)**			
	Intercept	2161	26.96 (25.58; 28.35)	$<2.0*10^{-16}$
	Age		0.03 (0.01; 0.05)	0.01
	Income		-0.31 (-0.55; -0.08)	0.01
	Education (years)			
	Intercept	2242	28.29 (26.60; 29.98)	$<2.0*10^{-16}$
	Age		0.03 (0.01; 0.05)	0.0001
	Education		-0.14 (-0.21; -0.07)	<0.01
Female	**Income (1000€/month)**			
	Intercept	2053	23.58 (21.73; 25.43)	$<2.0*10^{-16}$
	Age		0.09 (0.06; 0.12)	$4.3*10^{-10}$
	Income		-0.89 (-1.22; -0.57)	$9.3*10^{-8}$
	Education (years)			
	Intercept	2240	28.45 (25.99; 30.90)	$<2.0*10^{-16}$
	Age		0.07 (0.04; 0.10)	$2.6*10^{-6}$
	Education		-0.37 (-0.47; -0.27)	$6.8*10^{-13}$

Table s- 4 Age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) of the association of a BMI-associated genetic risk score (GRS_{BMI}) in sex-stratified linear regression models.

Model 2 BMI ~ GRS + age +sex				
Male		**n**	**β (95% CI)**	***p***
	Intercept	2251	21.94 (19.21; 24.66)	$<2.0*10^{-16}$
	Age		0.04 (0.02; 0.06)	0.001
	GRS		0.04 (0.02; 0.07)	0.001
Female		**n**	**β (95% CI)**	***p***
	Intercept	2242	8.30 (4.81; 11.79)	$3.3*10^{-6}$
	Age		0.10 (0.07; 0.13)	$6.6*10^{-13}$
	GRS		0.15 (0.11; 0.18)	$<2.0*10^{-16}$

Table s- 5 Sex- and age- adjusted effects and corresponding 95% confidence intervals (95% CI) for the association of indicators of socioeconomic status (SES; 1000€ income/month and years of education) and factors of SES-related health behavior (no physical inactivity, current smoking, alcohol consumption [Alc; per 100g/week]) on body mass index (BMI) in linear regression models, separately for income and education.

	Model 3 (n= 4147) BMI ~ SES + PA+ age + sex		**Model 4** (n= 4147) BMI ~ SES + S + age + sex		**Model 5** (n= 4057) BMI ~ SES + Alc + age + sex	
	β (95%-CI)	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***
Income (1000€/month)						
Intercept	25.04 (23.87; 26.21)	$< 2.0*10^{-16}$	26.58 (25.36; 27.79)	$<2.0*10^{-16}$	25.54 (24.25; 26.83)	$< 2.0*10^{-16}$
Age	0.06 (0.04; 0.08)	$8.7*10^{-11}$	0.05 (0.03; 0.07)	$1.9*10^{-7}$	0.06 (0.04; 0.08)	$3.7*10^{-10}$
Sex	-0.53 (-0.81; -0.25)	0.0002	-0.64 (-0.92; -0.37)	$5.6*10^{-6}$	-0.75 (-1.07; -0.42)	$6.1*10^{-6}$
Income	-0.51 (-0.70; -0.31)	$6.3*10^{-7}$	-0.63 (-0.83; -0.43)	$4.2*10^{-10}$	-0.60 (-0.82; -0.39)	$5.2*10^{-8}$
GRS	-	-	-	-	-	-
No physical activity	0.91 (0.63; 1.18)	$1.8*10^{-10}$	-	-	-	-
Current smoking	-	-	-0.97 (-1.30; -0.63)	$1.4*10^{-8}$	-	-
Alcohol consumption	-	-	-	-	-0.06 (-0.22; 0.09)	0.42
	Model 3 (n= 4411)		**Model 4** (n= 4411)		**Model 5** (n= 4305)	
Education (years)						
Intercept	27.85 (26.33; 29.37)	$<2.0*10^{-16}$	30.02 (28.47; 31.57)	$<2.0*10^{-16}$	28.55 (26.92; 30.19)	$< 2.0*10^{-16}$
Age	0.05 (0.04; 0.07)	$1.7*10^{-9}$	0.04 (0.02; 0.06)	$7.1*10^{-6}$	0.06 (0.04; 0.08)	$2.8*10^{-9}$
Sex	-0.82 (-1.10; -0.53)	$1.8*10^{-8}$	-0.98 (-1.26; -0.70)	$1.2*10^{-11}$	-1.07 (-1.39; -0.74)	$1.5*10^{-10}$
Education	-0.22 (-0.28; -0.16)	$7.8*10^{-13}$	-0.27 (-0.33; -0.21)	$<2.0*10^{-16}$	-0.25 (-0.32; -0.19)	$5.8*10^{-14}$
GRS	-	-	-	-	-	-
No physical activity	0.80 (0.53; 1.07)	$8.7*10^{-9}$	-	-	-	-
Current smoking	-	-	-1.02 (-1.34; -0.69)	$8.0*10^{-10}$	-	-
Alcohol consumption	-	-	-	-	-0.08 (-0.23; 0.07)	0.31

Table s- 6 Age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) in linear regression models including main effects and interaction terms of 1000€ income/month as an indicator of socioeconomic status (SES), a BMI-associated genetic risk score (GRS) and SEP-related health behaviors (no physical activity [PA], current smoking [S], alcohol consumption [Alc; per 100g/week]), stratified by sex.

		Model 6 (n= 2242) BMI ~ SES + age + GRS + GRS*SES		**Model 7** (n= 2124) BMI ~ SES + age + GRS + PA + GRS*SES + GRS*PA + SES*PA		**Model 8** (n= 2124) BMI ~ SES + age + GRS + S + GRS*SES + GRS*S + SES*S		**Model 9** (n= 2093) BMI ~ SES + age + GRS + Alc + GRS*SES + GRS*Alc + SES*Alc	
		β (95%-CI)	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***
Male	Intercept	17.67 (11.37; 23.97)	$4.3*10^{-8}$	20.40 (13.20; 27.60)	$2.8*10^{-8}$	20.50 (13.90; 27.11)	$1.4*10^{-9}$	17.65 (11.15; 24.15)	$1.1*10^{-7}$
	Age	0.03 (0.01; 0.05)	<0.01	0.03 (0.004; 0.05)	0.02	0.02 (-0.004; 0.04)	0.11	0.03 (0.01; 0.05)	<0.01
	Income	2.74 (-0.59; 6.06)	0.11	2.10 (-1.28; 5.47)	0.22	2.31 (-1.04; 5.65)	0.18	2.63 (-0.72; 5.98)	0.12
	GRS	0.10 (0.03; 0.17)	<0.01	0.08 (-0.001; 0.15)	0.05	0.08 (0.01; 0.15)	0.02	0.10 (0.03; 0.17)	<0.01
	No physical activity	-	-	-3.84 (-8.82; 1.14)	0.13	-	-	-	-
	Current smoking	-	-	-	-	-5.79 (-11.53; -0.06)	0.05	-	-
	Alcohol consumption	-	-	-	-	-	-	0.005 (-1.74; 1.75)	1.00
	GRS x Income	-0.03 (-0.07; 0.003)	0.07	-0.03 (-0.07; 0.01)	0.12	-0.03 (-0.07; 0.01)	0.10	-0.03 (-0.07; 0.003)	0.07
	GRS x PA	-	-	0.04 (-0.02; 0.09)	0.18	-	-	-	-
	GRS x S	-	-	-	-	0.04 (-0.02; 0.11)	0.16	-	-
	GRS x Alc	-	-	-	-	-	-	-0.002 (-0.02; 0.02)	0.81
	Income x PA	-	-	0.72 (0.25; 1.19)	<0.01	-	-	-	-
	Income x S	-	-	-	-	0.56 (0.04; 1.08)	0.04	-	-
	Income x Alc	-	-	-	-	-	-	0.11 (-0.05; 0.28)	0.17
		Model 6 (n= 2053)		**Model 7** (n= 2023)		**Model 8** (n= 2023)		**Model 9** (n= 1964)	
Female	Intercept	4.63 (-3.05; 12.31)	0.24	10.10 (1.52; 18.80)	0.02	7.51 (-0.41; 15.44)	0.06	4.94 (-2.84; 12.73)	0.21
	Age	0.09 (0.06; 0.12)	$3.0*10^{-10}$	0.09 (0.06; 0.12)	$2.0*10^{-9}$	0.07 (0.04; 0.10)	$1.3*10^{-6}$	0.09 (0.07; 0.12)	$1.4*10^{-10}$
	Income	3.08 (-1.42; 7.58)	0.18	2.05 (-2.50; 6.60)	0.38	2.64 (-1.88; 7.16)	0.25	2.71 (-1.91; 7.33)	0.25
	GRS	0.21 (0.13; 0.29)	$6.7*10^{-7}$	0.15 (0.06; 0.24)	<0.01	0.19 (0.11; 0.28)	$6.2*10^{-6}$	0.20 (0.12; 0.29)	$1.3*10^{-6}$
	No physical activity	-	-	-7.89 (-14.40; -1.35)	0.02	-	-	-	-
	Current smoking	-	-	-	-	-6.27 (-14.20; 1.65)	0.12	-	-
	Alcohol consumption	-	-	-	-	-	-	-0.66 (-7.88; 6.56)	0.86
	GRS x Income	-0.04 (-0.09; 0.01)	0.08	-0.03 (-0.08; 0.02)	0.19	-0.04 (-0.09; 0.01)	0.10	-0.04 (-0.09; 0.01)	0.12
	GRS x PA	-	-	0.09 (0.02; 0.16)	0.01	-	-	-	-
	GRS x S	-	-	-	-	0.04 (-0.04; 0.13)	0.33	-	-
	GRS x Alc	-	-	-	-	-	-	-0.01 (-0.01; 0.01)	0.88
	Income x PA	-	-	0.49 (-0.16; 1.14)	0.14	-	-	-	-
	Income x S	-	-	-	-	0.85 (0.09; 1.61)	0.03	-	-
	Income x Alc	-	-	-	-			0.43 (-0.17; 1.04)	0.16

Table s- 7 Age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) in linear regression models including main effects and interaction terms of years of education as an indicator of socioeconomic status (SES), a BMI-associated genetic risk score (GRS) and SEP-related health behaviors (no physical activity [PA], current smoking [S], alcohol consumption [Alc; per 100g/week]), stratified by sex.

		Model 6 (n= 2161) BMI ~ SES + age + GRS + GRS*SES		**Model 7** (n= 2203) BMI ~ SES + age + GRS + PA + GRS*SES + GRS*PA + SES*PA		**Model 8** (n= 2203) BMI ~ SES + age + GRS + S + GRS*SES + GRS*S + SES*S		**Model 9** (n= 2167) BMI ~ SES + age + GRS + Alc + GRS*SES + GRS*Alc + SES*Alc	
		β (95%-CI)	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***	**β (95%-CI)**	***p***
Male	Intercept	7.24 (-8.09; 22.57)	0.35	12.00 (-4.28; 28.28)	0.15	9.69 (-6.04; 25.42)	0.23	8.38 (-7.14; 23.90)	0.29
	Age	0.03 (0.01; 0.05)	<0.01	0.03 (0.01; 0.05)	<0.01	0.02 (-0.001; 0.04)	0.06	0.03 (0.01; 0.05)	<0.01
	Education	1.00 (-0.02; 2.02)	0.05	0.78 (-0.27; 1.82)	0.14	0.95 (-0.08; 1.98)	0.07	0.93 (-0.10; 1.96)	0.08
	GRS	0.23 (0.06; 0.40)	0.01	0.18 (0.0003; 0.35)	0.05	0.22 (0.05; 0.39)	0.01	0.22 (0.05; 0.39)	0.01
	Physical activity	-	-	-3.66 (-8.97; 1.65)	0.18	-	-	-	-
	Current smoking	-	-	-	-	-5.72 (-11.87; 0.43)	0.07	-	-
	Alcohol consumption	-	-	-	-	-	-	-0.22 (-2.08; 1.65)	0.82
	GRS x Education	-0.01 (-0.02; -0.001)	0.03	-0.01 (-0.02; 0.001)	0.08	-0.01 (-0.02; -0.001)	0.03	-0.01 (-0.02; -0.001)	0.04
	GRS x PA	-	-	0.03 (-0.02; 0.09)	0.21	-	-	-	-
	GRS x S	-	-	-	-	0.03 (-0.03; 0.09)	0.35	-	-
	GRS x Alc	-	-	-	-	-	-	-0.0001 (-0.02; 0.02)	0.99
	Education x PA	-	-	0.09 (-0.06; 0.23)	0.24	-	-	-	-
	Education x S	-	-	-	-	0.15 (-0.02; 0.32)	0.08	-	-
	Education x Alc	-	-	-	-	-	-	0.01 (-0.04; 0.07)	0.62
		Model 6 n= 2240		**Model 7** (n= 2208)		**Model 8** (n= 2208)		**Model 9** (n= 2138)	
Female	Intercept	-5.28 (-23.53; 12.98)	0.57	1.44 (-17.63; 20.52)	0.88	-1.49 (-19.83; 16.86)	0.87	-4.24 (-22.90; 14.43)	0.66
	Age	0.07 (0.04; 0.10)	$1.4*10^{-6}$	0.07 (0.04; 0.09)	$4.2*10^{-6}$	0.05 (0.02; 0.08)	<0.01	0.07 (0.04; 0.10)	$6.3*10^{-7}$
	Education	1.20 (-0.15; 2.55)	0.08	0.93 (-0.44; 2.30)	0.18	1.11 (-0.24; 2.47)	0.11	1.09 (-0.29; 2.46)	0.12
	GRS	0.37 (0.17; 0.57)	<0.001	0.29 (0.08; 0.50)	0.01	0.35 (0.15; 0.55)	0.001	0.36 (0.15; 0.56)	0.001
	Physical activity	-	-	-6.93 (-13.81; -0.06)	0.05	-	-	-	-
	Current smoking	-	-	-	-	-9.63 (-17.82; -1.43)	0.02	-	-
	Alcohol consumption	-	-	-	-	-	-	-0.13 (-7.64; 7.38)	0.97
	GRS x Education	-0.02 (-0.03; -0.002)	0.02	-0.01 (-0.03; 0.001)	0.06	-0.02 (-0.03; -0.002)	0.03	-0.02 (-0.03; 0.001)	0.04
	GRS x PA	-	-	0.07 (0.01; 0.14)	0.04	-	-	-	-
	GRS x S	-	-	-	-	0.05 (-0.03; 0.13)	0.26	-	-
	GRS x Alc	-	-	-	-	-	-	-0.02 (-0.09; 0.06)	0.68
	Education x PA	-	-	0.08 (-0.11; 0.27)	0.41	-	-	-	-
	Education x S	-	-	-	-	0.31 (0.07; 0.55)	0.01	-	-
	Education x Alc	-	-	-	-	-	-	0.08 (-0.11; 0.28)	0.40

Table s- 8 Sex- and age- adjusted effects and corresponding 95% confidence intervals (95% CI) on body mass index (BMI) in linear regression models including main effects and interaction terms of indicators of socioeconomic position (SEP; years of education and 1000€ income/month) and a BMI-associated genetic risk score (GRS, separately for income and education within a reduced study population.

	Model 1 (n= 3545) BMI ~ SES + age + sex		**Model 2** (n= 3780) BMI ~ GRS + age + sex		**Model 6** (n= 3545) BMI ~ SES + GRS + GRS*SES + age + sex	
	β (95% CI)	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Income (1000€/month)						
Income	-0.61 (-0.83; -0.40)	$2.6*10^{-8}$	-	-	3.29 (0.33; 6.26)	0.03
GRS	-	-	0.10 (0.07; 0.12)	$5.0*10^{-16}$	0.16 (0.10; 0.22)	$4.0*10^{-8}$
GRS x Income	-	-	-	-	-0.04 (-0.08; -0.01)	0.01
	Model 1 (n= 3770)		**Model 2** (n= 3780)		**Model 6** (n= 3770)	
Education (year)						
Education	-0.25 (-0.32; -0.19)	$2.4*10^{-14}$	-	-	1.40 (0.54; 2.26)	0.001
GRS	-	-	0.10 (0.07; 0.12)	$5.0*10^{-16}$	0.35 (0.21; 0.48)	3.8*10-7
GRS x Education	-	-	-	-	-0.02 (-0.03; -0.01)	<0.001

Table s- 9 (Sex-) and age- adjusted (and sex-stratified) effects and corresponding 95% confidence intervals (95% CI) for the association of a weighted genetic risk score (wGRS) on body mass index (BMI) in linear regression models (stratified by sex).

		n	$ß_{wGRS}$ (95% CI)	*p*
All	wGRS on BMI	4422	0.10 (0.07; 0.12)	$2.00*10^{-16}$
Male	wGRS on BMI	2212	0.05 (0.03; 0.08)	$5.22*10^{-5}$
Female	wGRS on BMI	2210	0.14 (0.11; 0.17)	$2.00*10^{-16}$

Table s- 10 (Sex-) and age-adjusted effects and corresponding 95% confidence interval (95% CI) for the interaction of a weighted BMI-associated genetic risk score (wGRS) and and income (per 1000€ income/month) and education (per year) as indicators of socioeconomic status (SES) by on body mass index (BMI) in linear regression models (stratified by sex).

		n	$ß_{wGRSxSES}$ (95% CI)	*p*
All				
	wGRS x Income	4147	-0.04 (-0.01; -0.01)	0.02
	wGRS x Education	4411	-0.02 (-0.03; -0.01)	$7.98*10^{-5}$
Male				
	wGRS x Income	2124	-0.03 (-0.07; 0.01)	0.16
	wGRS x Education	2202	-0.01 (-0.02; -0.01)	0.03
Female				
	wGRS x Income	2023	-0.05 (-0.09; 0.01)	0.15
	wGRS x Education	2208	-0.02 (-0.03; -0.001)	0.04

Table s- 11 (Sex-) and age- adjusted (and sex-stratified) effects and corresponding 95% confidence intervals (95% CI) of the genetic effect on body mass index (BMI), stratified by education groups and income quartiles.

	n	$ß_{wGRS}$ (95% CI)	*p*
Income (1000€/month)			
Lowest Quartile	1120	0.14 (0.10; 0.18)	$3.93*10^{-10}$
Second Quartile	1035	0.11 (0.07; 0.16)	$1.54*10^{-7}$
Third Quartile	1110	0.05 (0.01; 0.09)	0.02
Highest Quartile	933	0.06 (0.02; 0.10)	0.005
Education (year)			
≤ 10	504	0.24 (0.17; 0.31)	$2.09*10^{-11}$
11-13	2446	0.08 (0.06; 0.11)	$2.00*10^{-9}$
14-17	989	0.06 (0.02; 0.10)	0.004
≥18	972	0.05 (-0.01; 0.10)	0.10

Table s-12 Age- and sex-adjusted effects and corresponding 95% confidence interval (95% CI) of the interaction between each body mass index (BMI) associated single nucleotide polymorphism (SNP) and income (per 1000€/month) in separate linear regression models, sorted by ascending effect size estimates.

Chr:Position*	Locus	SNP	Risk Allele	$ß_{SNPxInc}$	95 % CI		*p*
					Lower	Upper	
3:85890280	CADM2	rs13078960	G	-0.3181	-0.66	0.03	0.07
13:65103705	MIR548X2	rs9540493	A	-0.3124	-0.58	-0.04	0.02
19:39001372	KCTD15	rs29941	G	-0.3010	-0.60	0.00	0.05
18:55034299	GRP	rs7243357	T	-0.2806	-0.67	0.11	0.16
14:24998019	STXBP6	rs10132280	C	-0.2630	-0.57	0.05	0.10
11:43820854	HSD17B12	rs2176598	T	-0.2604	-0.58	0.06	0.11
16:3567359	NLRC3	rs758747	T	-0.2269	-0.55	0.10	0.18
2:164275935	FIGN	rs1460676	C	-0.2071	-0.58	0.17	0.28
13:26915782	MTIF3	rs9581855 †	A	-0.2050	-0.57	0.16	0.27
4:145878514	HHIP	rs11727676	T	-0.1954	-0.67	0.28	0.42
4:44877284	GNPDA2	rs10938397	G	-0.1917	-0.47	0.09	0.18
18:19358886	C18orf8	rs1808579	C	-0.1907	-0.47	0.09	0.18
5:153518086	GALNT10	rs7715256	G	-0.1900	-0.47	0.09	0.19
6:34671142	C6orf106	rs205262	G	-0.1841	-0.49	0.12	0.24
7:75001105	HIP1	rs1167827	G	-0.1756	-0.45	0.10	0.22
18:38401669	LOC284260	rs7239883	G	-0.1609	-0.45	0.12	0.27
19:50894012	QPCTL	rs2287019	C	-0.1523	-0.49	0.18	0.37
8:85242264	RALYL	rs2033732	C	-0.1505	-0.47	0.17	0.35
16:28240912	SBK1	rs2650492	A	-0.1481	-0.44	0.15	0.33
3:187306698	ETVM	rs1516725	C	-0.1322	-0.54	0.28	0.53
10:104859028	NT5C2	rs11191560	C	-0.1285	-0.59	0.33	0.58
2:207963763	CREB1	rs17203016	G	-0.1264	-0.48	0.23	0.48
19:18315825	PGPEP1	rs17724992	A	-0.1263	-0.44	0.19	0.43
16:28796987	ATP2A1	rs3888190	A	-0.1188	-0.40	0.17	0.41
19:50087459	TOMM40	rs2075650	A	-0.1175	-0.52	0.28	0.57
14:28806589	PRKD1	rs12885454	C	-0.1089	-0.40	0.18	0.46
4:103407732	SLC39A8	rs13107325	T	-0.1084	-0.69	0.47	0.71
16:52361075	FTO	rs1558902	A	-0.1038	-0.39	0.18	0.48
9:110972163	EPB41L4B	rs6477694	C	-0.0886	-0.38	0.20	0.55
6:162953340	PARK2	rs13191362	A	-0.0878	-0.55	0.38	0.71
1:49362434	AGBL4	rs657452	A	-0.0855	-0.37	0.20	0.55
6:50877777	TFAP2B	rs2207139	G	-0.0828	-0.43	0.27	0.64
2:26782315	KCNK3	rs11126666	A	-0.0723	-0.39	0.24	0.65
9:28404339	LINGO2	rs10968576	G	-0.0690	-0.38	0.24	0.67

6:137717234	IFNGR1	rs13201877	G	-0.0665	-0.44	0.31	0.73
16:19842890	GPRC5B	rs12446632	G	-0.0560	-0.44	0.33	0.77
11:8630515	TRIM66	rs4256980	G	-0.0492	-0.34	0.24	0.74
7:95007450	ASB4	rs6465468	T	-0.0419	-0.34	0.25	0.78
3:61211502	FHIT	rs2365389	C	-0.0374	-0.33	0.25	0.80
6:120227364	LOC285762	rs9374842	T	-0.0355	-0.37	0.30	0.83
1:200050910	NAV1	rs2820292	C	-0.0330	-0.31	0.25	0.82
17:1951886	SMG6	rs9914578	G	-0.0318	-0.38	0.32	0.86
12:121347850	CLIP1	rs11057405	G	-0.0310	-0.46	0.40	0.89
4:77315142	SCARB2	rs17001561 †	A	-0.0284	-0.42	0.36	0.89
19:52260843	ZC3H4	rs3810291	A	-0.0269	-0.32	0.27	0.86
1:78219349	FUBP1	rs12401738	A	-0.0266	-0.32	0.27	0.86
2:62906552	EHBP1	rs11688816	G	-0.0249	-0.30	0.25	0.86
13:78478920	MIR548A2	rs1441264	A	-0.0140	-0.30	0.27	0.92
1:50332407	ELAVL4	rs11583200	C	-0.0112	-0.30	0.28	0.94
9:15624326	C9orf93	rs4740619	T	0.0089	-0.27	0.29	0.95
7:93568420	CALCR	rs9641123 †	C	0.0146	-0.29	0.32	0.93
1:7477478	FPGT-TNNI3K	rs12566985	G	0.0178	-0.27	0.31	0.90
10:102385430	HIF1AN	rs17094222	C	0.0228	-0.32	0.37	0.90
6:40456631	TDRG1	rs2033529	G	0.0301	-0.27	0.33	0.85
5:75050998	POC5	rs2112347	T	0.0328	-0.26	0.32	0.83
1:176156103	SEC16B	rs543874	G	0.0415	-0.31	0.39	0.81
8:76969685	HNF4G	rs17405819	T	0.0433	-0.26	0.35	0.78
3:141587171	RASA2	rs2035935 †	G	0.0460	-0.53	0.62	0.88
8:81538012	ZBTB10	rs16907751	C	0.0463	-0.41	0.50	0.84
21:39213610	ETS2	rs2836754	C	0.0465	-0.24	0.33	0.75
11:114527614	CADM1	rs12286929	G	0.0475	-0.23	0.33	0.74
20:50521269	ZFP64	rs6091540	C	0.0561	-0.26	0.38	0.73
17:76230166	RPTOR	rs12940622	G	0.0571	-0.22	0.34	0.69
2:59159129	LINC01122	rs1016287	T	0.0595	-0.25	0.37	0.71
7:76446079	PMS2L11	rs2245368	C	0.0625	-0.32	0.44	0.75
17:5223976	RABEP1	rs1000940	G	0.0645	-0.24	0.37	0.68
2:622348	TMEM18	rs13021737	G	0.0687	-0.31	0.44	0.72
12:48533735	BCDIN3D	rs7138803	A	0.0749	-0.21	0.36	0.61
15:70881044	LOC100287559	rs7164727	T	0.0835	-0.22	0.38	0.59
2:142759755	LRP1B	rs2121279	T	0.0866	-0.32	0.50	0.68
1:96696685	PTBP2	rs11165643	T	0.0934	-0.19	0.37	0.52
11:47607569	MTCH2	rs3817334	T	0.0953	-0.18	0.37	0.50
10:87400884	GRID1	rs7899106	G	0.1094	-0.56	0.78	0.75
6:109084356	FOXO3	rs9400239	C	0.1151	-0.18	0.41	0.44

3:25081441	RARB	rs6804842	G	0.1153	-0.16	0.39	0.41
16:47620091	CBLN1	rs2080454	C	0.1221	-0.16	0.41	0.40
2:219057996	USP37	rs492400	C	0.1308	-0.16	0.42	0.38
2:181259207	UBE2E3	rs1528435	T	0.1377	-0.15	0.42	0.35
1:72523773	NEGR1	rs3101336	C	0.1411	-0.15	0.43	0.34
15:49535902	DMXL2	rs3736485	A	0.1530	-0.13	0.43	0.28
15:65864222	MAP2K5	rs16951275	T	0.1547	-0.17	0.48	0.36
9:128500735	LMX1B	rs10733682	A	0.1931	-0.09	0.47	0.18
9:119418304	TLR4	rs1928295	T	0.2011	-0.08	0.48	0.16
16:29922838	INO80E	rs4787491	G	0.2076	-0.07	0.48	0.14
11:27641093	BDNF	rs11030104	A	0.2115	-0.13	0.55	0.22
14:29584863	PRKD1	rs11847697	T	0.2290	-0.44	0.90	0.50
2:25003800	ADCY3	rs10182181	G	0.2291	-0.05	0.50	0.10
14:78969207	NRXN3	rs7141420	T	0.2460	-0.04	0.53	0.09
1:47457264	TAL1	rs977747	T	0.2507	-0.04	0.54	0.09
2:213121476	ERBB4	rs7599312	G	0.2507	-0.06	0.56	0.12
10:114748339	TCF7L2	rs7903146	C	0.2603	-0.05	0.57	0.10
13:53000207	OLFM4	rs12429545	A	0.2918	-0.13	0.72	0.18
16:31037396	KAT8	rs9925964	A	0.2997	0.01	0.59	0.04
1:109956211	GNAT2	rs17024393	C	0.3022	-0.39	1.00	0.39
18:55980115	MC4R	rs6567160	C	0.3063	-0.01	0.62	0.06
3:81874802	GBE1	rs3849570	A	0.3684	0.07	0.66	0.01
2:226801046	LOC646736	rs2176040	A	0.3821	0.10	0.66	0.01

*Position of build 36, (LD r^2>0.9); † proxy SNPs (rs2035935 as a proxy for rs16851483, rs17001561 as a proxy for rs17001654 and rs9581855 as a proxy for rs12016871).

Table s-13 Age- and sex-adjusted effects and corresponding 95% confidence interval (95% CI) of the interaction between each body mass index (BMI) associated single nucleotide polymorphism (SNP) and education (per year) in separate linear regression models, sorted by ascending effect size estimates.

Chr:Position*	Locus	SNP	Risk Allele	$ß_{SNPxEdu}$	95 % CI		*p*
					Lower	Upper	
12:121347850	CLIP1	rs11057405	G	-0.1650	-0.29	-0.04	0.01
16:3567359	NLRC3	rs758747	T	-0.0898	-0.18	0.001	0.05
13:65103705	MIR548X2	rs9540493	A	-0.0861	-0.17	-0.01	0.03
19:50894012	QPCTL	rs2287019	C	-0.0850	-0.18	0.01	0.10
5:153518086	GALNT10	rs7715256	G	-0.0793	-0.16	0.00	0.05
14:28806589	PRKD1	rs12885454	C	-0.0747	-0.16	0.01	0.08
3:141587171	RASA2	rs2035935 †	G	-0.0631	-0.22	0.10	0.44
7:75001105	HIP1	rs1167827	G	-0.0625	-0.14	0.02	0.13
14:24998019	STXBP6	rs10132280	C	-0.0617	-0.15	0.03	0.17
3:25081441	RARB	rs6804842	G	-0.0613	-0.14	0.02	0.13
11:8630515	TRIM66	rs4256980	G	-0.0612	-0.14	0.02	0.14
4:103407732	SLC39A8	rs13107325	T	-0.0588	-0.23	0.11	0.50
9:28404339	LINGO2	rs10968576	G	-0.0569	-0.14	0.03	0.20
19:39001372	KCTD15	rs29941	G	-0.0510	-0.13	0.03	0.23
1:50332407	ELAVL4	rs11583200	C	-0.0466	-0.13	0.04	0.27
2:26782315	KCNK3	rs11126666	A	-0.0378	-0.13	0.06	0.43
10:102385430	HIF1AN	rs17094222	C	-0.0370	-0.14	0.07	0.48
4:44877284	GNPDA2	rs10938397	G	-0.0360	-0.12	0.05	0.38
16:28796987	ATP2A1	rs3888190	A	-0.0359	-0.12	0.05	0.40
8:85242264	RALYL	rs2033732	C	-0.0341	-0.13	0.06	0.46
6:137717234	IFNGR1	rs13201877	G	-0.0337	-0.15	0.08	0.57
2:207963763	CREB1	rs17203016	G	-0.0331	-0.14	0.07	0.53
17:1951886	SMG6	rs9914578	G	-0.0330	-0.13	0.06	0.51
11:114527614	CADM1	rs12286929	G	-0.0321	-0.11	0.05	0.44
11:43820854	HSD17B12	rs2176598	T	-0.0312	-0.12	0.06	0.50
15:49535902	DMXL2	rs3736485	A	-0.0299	-0.11	0.05	0.46
6:50877777	TFAP2B	rs2207139	G	-0.0252	-0.13	0.08	0.63
1:96696685	PTBP2	rs11165643	T	-0.0235	-0.10	0.06	0.57
18:55034299	GRP	rs7243357	T	-0.0231	-0.13	0.08	0.67
7:95007450	ASB4	rs6465468	T	-0.0223	-0.11	0.06	0.61
10:104859028	NT5C2	rs11191560	C	-0.0220	-0.15	0.11	0.74
9:15624326	C9orf93	rs4740619	T	-0.0217	-0.10	0.06	0.60
7:76446079	PMS2L11	rs2245368	C	-0.0212	-0.13	0.09	0.70
6:40456631	TDRG1	rs2033529	G	-0.0203	-0.11	0.07	0.65
13:78478920	MIR548A2	rs1441264	A	-0.0182	-0.10	0.06	0.67
8:76969685	HNF4G	rs17405819	T	-0.0182	-0.11	0.07	0.69
4:145878514	HHIP	rs11727676	T	-0.0151	-0.15	0.12	0.83
3:61211502	FHIT	rs2365389	C	-0.0142	-0.09	0.07	0.73

18:19358886	C18orf8	rs1808579	C	-0.0133	-0.09	0.07	0.74
16:28240912	SBK1	rs2650492	A	-0.0131	-0.10	0.07	0.77
6:34671142	C6orf106	rs205262	G	-0.0126	-0.10	0.08	0.78
16:52361075	FTO	rs1558902	A	-0.0113	-0.09	0.07	0.78
3:187306698	ETVM	rs1516725	C	-0.0087	-0.13	0.11	0.89
6:120227364	LOC285762	rs9374842	T	-0.0087	-0.10	0.09	0.86
16:19842890	GPRC5B	rs12446632	G	-0.0041	-0.12	0.11	0.95
3:85890280	CADM2	rs13078960	G	-0.0024	-0.10	0.10	0.96
1:49362434	AGBL4	rs657452	A	-0.0002	-0.08	0.08	1.00
4:77315142	SCARB2	rs17001561 †	A	0.0013	-0.11	0.11	0.98
14:29584863	PRKD1	rs11847697	T	0.0014	-0.20	0.21	0.99
1:200050910	NAV1	rs2820292	C	0.0029	-0.08	0.08	0.94
13:26915782	MTIF3	rs9581855 †	A	0.0033	-0.10	0.11	0.95
1:78219349	FUBP1	rs12401738	A	0.0037	-0.08	0.09	0.93
15:65864222	MAP2K5	rs16951275	T	0.0045	-0.09	0.10	0.93
19:18315825	PGPEP1	rs17724992	A	0.0074	-0.09	0.10	0.88
8:81538012	ZBTB10	rs16907751	C	0.0076	-0.12	0.13	0.91
12:48533735	BCDIN3D	rs7138803	A	0.0087	-0.07	0.09	0.83
21:39213610	ETS2	rs2836754	C	0.0124	-0.07	0.10	0.77
5:75050998	POC5	rs2112347	T	0.0181	-0.07	0.10	0.67
2:219057996	USP37	rs492400	C	0.0203	-0.06	0.10	0.63
2:59159129	LINC01122	rs1016287	T	0.0211	-0.07	0.11	0.65
20:50521269	ZFP64	rs6091540	C	0.0224	-0.07	0.11	0.63
9:110972163	EPB41L4B	rs6477694	C	0.0235	-0.06	0.11	0.58
17:5223976	RABEP1	rs1000940	G	0.0236	-0.06	0.11	0.60
2:164275935	FIGN	rs1460676	C	0.0265	-0.08	0.13	0.62
2:142759755	LRP1B	rs2121279	T	0.0323	-0.08	0.14	0.57
18:38401669	LOC284260	rs7239883	G	0.0329	-0.05	0.11	0.43
11:47607569	MTCH2	rs3817334	T	0.0331	-0.05	0.11	0.42
7:93568420	CALCR	rs9641123	C	0.0333	-0.05	0.12	0.45
16:31037396	KAT8	rs9925964	A	0.0361	-0.05	0.12	0.39
2:25003800	ADCY3	rs10182181	G	0.0389	-0.04	0.12	0.33
2:62906552	EHBP1	rs11688816	G	0.0438	-0.04	0.12	0.29
2:181259207	UBE2E3	rs1528435	T	0.0450	-0.04	0.13	0.29
13:53000207	OLFM4	rs12429545	A	0.0467	-0.07	0.17	0.45
15:70881044	LOC100287559	rs7164727	T	0.0478	-0.04	0.13	0.28
16:47620091	CBLN1	rs2080454	C	0.0484	-0.03	0.13	0.25
1:47457264	TAL1	rs977747	T	0.0503	-0.03	0.14	0.25
14:78969207	NRXN3	rs7141420	T	0.0509	-0.03	0.13	0.22
9:128500735	LMX1B	rs10733682	A	0.0538	-0.03	0.13	0.19
1:7477478	FPGT-TNNI3K	rs12566985	G	0.0572	-0.02	0.14	0.17
10:114748339	TCF7L2	rs7903146	C	0.0587	-0.03	0.15	0.19
16:29922838	INO80E	rs4787491	G	0.0593	-0.02	0.14	0.15
19:50087459	TOMM40	rs2075650	A	0.0637	-0.05	0.18	0.27

19:52260843	ZC3H4	rs3810291	A	0.0663	-0.02	0.15	0.14
1:72523773	NEGR1	rs3101336	C	0.0685	-0.02	0.15	0.11
6:162953340	PARK2	rs13191362	A	0.0691	-0.06	0.20	0.31
2:622348	TMEM18	rs13021737	G	0.0736	-0.03	0.18	0.16
6:109084356	FOXO3	rs9400239	C	0.0738	-0.01	0.16	0.10
2:213121476	ERBB4	rs7599312	G	0.0748	-0.01	0.16	0.10
18:55980115	MC4R	rs6567160	C	0.0752	-0.02	0.17	0.11
2:226801046	LOC646736	rs2176040	A	0.0785	-0.004	0.16	0.06
17:76230166	RPTOR	rs12940622	G	0.0955	0.01	0.18	0.02
9:119418304	TLR4	rs1928295	T	0.0973	0.02	0.18	0.02
11:27641093	BDNF	rs11030104	A	0.1016	0.002	0.20	0.05
3:81874802	GBE1	rs3849570	A	0.1122	0.03	0.20	0.01
10:87400884	GRID1	rs7899106	G	0.1492	-0.04	0.34	0.13
1:176156103	SEC16B	rs543874	G	0.1539	0.05	0.26	0.004
1:109956211	GNAT2	rs17024393	C	0.1983	0.00	0.40	0.05

*Position of build 36, (LD r^2>0.9); † proxy SNPs (rs2035935 as a proxy for rs16851483, rs17001561 as a proxy for rs17001654 and rs9581855 as a proxy for rs12016871).

Table s-14 Age- and sex-adjusted effects and corresponding 95% confidence interval (95% CI) of the interaction between each body mass index (BMI) associated single nucleotide polymorphism (SNP) and physical activity (PA) in separate linear regression models, sorted by ascending effect size estimates.

Chr:Position*	Locus	SNP	Risk Allele	$ß_{SNPxPA}$	95 % CI		*p*
					Lower	Upper	
11:43820854	HSD17B12	rs2176598	T	0.5491	0.11	0.99	0.02
18:55980115	MC4R	rs6567160	C	0.5306	0.08	0.98	0.02
10:87400884	GRID1	rs7899106	G	0.4074	-0.50	1.31	0.38
14:29584863	PRKD1	rs11847697	T	0.4027	-0.55	1.36	0.41
6:50877777	TFAP2B	rs2207139	G	0.3892	-0.10	0.88	0.12
18:55034299	GRP	rs7243357	T	0.3374	-0.18	0.86	0.20
3:141587171	RASA2	rs2035935 †	G	0.3087	-0.47	1.09	0.44
5:153518086	GALNT10	rs7715256	G	0.2800	-0.11	0.67	0.16
14:28806589	PRKD1	rs12885454	C	0.2635	-0.14	0.67	0.20
11:8630515	TRIM66	rs4256980	G	0.2613	-0.14	0.66	0.20
7:95007450	ASB4	rs6465468	T	0.2463	-0.16	0.66	0.24
6:120227364	LOC285762	rs9374842	T	0.2381	-0.20	0.68	0.29
12:121347850	CLIP1	rs11057405	G	0.2291	-0.39	0.85	0.47
10:102385430	HIF1AN	rs17094222	C	0.2195	-0.26	0.70	0.37
17:5223976	RABEP1	rs1000940	G	0.2115	-0.21	0.64	0.33
7:75001105	HIP1	rs1167827	G	0.1729	-0.21	0.56	0.38
2:25003800	ADCY3	rs10182181	G	0.1651	-0.22	0.55	0.40
19:39001372	KCTD15	rs29941	G	0.1578	-0.25	0.57	0.45
4:77315142	SCARB2	rs17001654†	A	0.1561	-0.37	0.69	0.56
1:49362434	AGBL4	rs657452	A	0.1558	-0.24	0.55	0.44
2:207963763	CREB1	rs17203016	G	0.1552	-0.32	0.63	0.52
18:38401669	LOC284260	rs7239883	G	0.1390	-0.26	0.53	0.49
1:109956211	GNAT2	rs17024393	C	0.1320	-0.87	1.13	0.80
2:181259207	UBE2E3	rs1528435	T	0.1161	-0.28	0.51	0.57
1:78219349	FUBP1	rs12401738	A	0.1140	-0.28	0.51	0.57
2:26782315	KCNK3	rs11126666	A	0.1093	-0.32	0.54	0.62
16:28240912	SBK1	rs2650492	A	0.1031	-0.31	0.51	0.62
3:81874802	GBE1	rs3849570	A	0.0795	-0.32	0.48	0.69
9:119418304	TLR4	rs1928295	T	0.0697	-0.31	0.45	0.72
5:75050998	POC5	rs2112347	T	0.0685	-0.33	0.47	0.74
18:19358886	C18orf8	rs1808579	C	0.0676	-0.32	0.45	0.73
13:78478920	MIR548A2	rs1441264	A	0.0638	-0.33	0.46	0.75
15:70881044	LOC100287559	rs7164727	T	0.0632	-0.35	0.48	0.77
16:47620091	CBLN1	rs2080454	C	0.0613	-0.34	0.46	0.76

14:78969207	NRXN3	rs7141420	T	0.0576	-0.33	0.45	0.77
9:28404339	LINGO2	rs10968576	G	0.0549	-0.36	0.47	0.79
8:76969685	HNF4G	rs17405819	T	0.0511	-0.37	0.47	0.81
16:28796987	ATP2A1	rs3888190	A	0.0508	-0.34	0.44	0.80
3:61211502	FHIT	rs2365389	C	0.0507	-0.34	0.44	0.80
1:176156103	SEC16B	rs543874	G	0.0441	-0.46	0.54	0.86
7:93568420	CALCR	rs9641123†	C	0.0434	-0.38	0.47	0.84
19:50087459	TOMM40	rs2075650	A	0.0381	-0.50	0.57	0.89
19:50894012	QPCTL	rs2287019	C	0.0239	-0.45	0.50	0.92
8:81538012	ZBTB10	rs16907751	C	0.0231	-0.60	0.64	0.94
1:96696685	PTBP2	rs11165643	T	0.0192	-0.37	0.41	0.92
3:85890280	CADM2	rs13078960	G	0.0163	-0.47	0.50	0.95
4:44877284	GNPDA2	rs10938397	G	0.0143	-0.37	0.40	0.94
1:50332407	ELAVL4	rs11583200	C	0.0119	-0.38	0.40	0.95
19:18315825	PGPEP1	rs17724992	A	-0.0028	-0.44	0.44	0.99
2:62906552	EHBP1	rs11688816	G	-0.0132	-0.40	0.38	0.95
2:226801046	LOC646736	rs2176040	A	-0.0148	-0.41	0.38	0.94
11:114527614	CADM1	rs12286929	G	-0.0225	-0.41	0.37	0.91
15:65864222	MAP2K5	rs16951275	T	-0.0277	-0.48	0.42	0.90
10:114748339	TCF7L2	rs7903146	C	-0.0300	-0.46	0.40	0.89
16:3567359	NLRC3	rs758747	T	-0.0396	-0.48	0.40	0.86
1:72523773	NEGR1	rs3101336	C	-0.0432	-0.44	0.35	0.83
9:110972163	EPB41L4B	rs6477694	C	-0.0446	-0.44	0.35	0.82
20:50521269	ZFP64	rs6091540	C	-0.0490	-0.49	0.40	0.83
11:27641093	BDNF	rs11030104	A	-0.0550	-0.52	0.41	0.82
10:104859028	NT5C2	rs11191560	C	-0.0556	-0.69	0.58	0.86
16:19842890	GPRC5B	rs12446632	G	-0.0636	-0.61	0.48	0.82
4:103407732	SLC39A8	rs13107325	T	-0.0640	-0.86	0.74	0.88
6:40456631	TDRG1	rs2033529	G	-0.0691	-0.49	0.35	0.75
2:142759755	LRP1B	rs2121279	T	-0.0733	-0.62	0.47	0.79
14:24998019	STXBP6	rs10132280	C	-0.0787	-0.50	0.34	0.71
15:49535902	DMXL2	rs3736485	A	-0.0927	-0.48	0.29	0.64
6:109084356	FOXO3	rs9400239	C	-0.0957	-0.51	0.32	0.65
2:164275935	FIGN	rs1460676	C	-0.1047	-0.61	0.40	0.69
6:162953340	PARK2	rs13191362	A	-0.1105	-0.75	0.53	0.74
13:65103705	MIR548X2	rs9540493	A	-0.1154	-0.50	0.27	0.55
2:59159129	LINC01122	rs1016287	T	-0.1177	-0.55	0.32	0.59
9:128500735	LMX1B	rs10733682	A	-0.1281	-0.51	0.25	0.51
13:26915782	MTIF3	rs12016871†	A	-0.1597	-0.67	0.35	0.54
3:187306698	ETVM	rs1516725	C	-0.1634	-0.73	0.41	0.57

11:47607569	MTCH2	rs3817334	T	-0.1680	-0.56	0.22	0.40
17:1951886	SMG6	rs9914578	G	-0.1706	-0.65	0.31	0.48
9:15624326	C9orf93	rs4740619	T	-0.1727	-0.56	0.22	0.39
16:52361075	FTO	rs1558902	A	-0.1827	-0.57	0.20	0.35
8:85242264	RALYL	rs2033732	C	-0.1897	-0.63	0.25	0.39
21:39213610	ETS2	rs2836754	C	-0.1905	-0.58	0.20	0.34
12:48533735	BCDIN3D	rs7138803	A	-0.1935	-0.58	0.20	0.33
2:213121476	ERBB4	rs7599312	G	-0.2054	-0.63	0.22	0.34
1:7477478	FPGT-TNNI3K	rs12566985	G	-0.2098	-0.60	0.18	0.29
6:34671142	C6orf106	rs205262	G	-0.2117	-0.64	0.21	0.33
17:76230166	RPTOR	rs12940622	G	-0.2274	-0.61	0.16	0.25
16:29922838	INO80E	rs4787491	G	-0.2500	-0.63	0.13	0.20
3:25081441	RARB	rs6804842	G	-0.2507	-0.64	0.14	0.21
6:137717234	IFNGR1	rs13201877	G	-0.3247	-0.86	0.21	0.23
1:47457264	TAL1	rs977747	T	-0.3280	-0.73	0.07	0.11
1:200050910	NAV1	rs2820292	C	-0.3695	-0.75	0.01	0.06
19:52260843	ZC3H4	rs3810291	A	-0.3762	-0.79	0.03	0.07
2:219057996	USP37	rs492400	C	-0.3859	-0.78	0.01	0.05
16:31037396	KAT8	rs9925964	A	-0.3971	-0.80	0.00	0.05
13:53000207	OLFM4	rs12429545	A	-0.4419	-1.03	0.15	0.14
2:622348	TMEM18	rs13021737	G	-0.5150	-1.02	-0.01	0.05
7:76446079	PMS2L11	rs2245368	C	-0.5775	-1.09	-0.06	0.03
4:145878514	HHIP	rs11727676	T	-0.7487	-1.42	-0.08	0.03

*Position of build 36, (LD r^2>0.9); † proxy SNPs (rs2035935 as a proxy for rs16851483, rs17001561 as a proxy for rs17001654 and rs9581855 as a proxy for rs12016871).

Table s-15 Age- and sex-adjusted effects and corresponding 95% confidence interval (95% CI) of the interaction between each body mass index (BMI) associated single nucleotide polymorphism (SNP) and smoking (S) in separate linear regression models, sorted by ascending effect size estimates.

Chr:Position*	Locus	SNP	Risk Allele	$ß_{SNPxS}$	95 % CI		*p*
					Lower	Upper	
4:103407732	SLC39A8	rs13107325	T	0.6650	-0.25	1.58	0.16
18:55980115	MC4R	rs6567160	C	0.5728	0.05	1.09	0.03
19:39001372	KCTD15	rs29941	G	0.4543	-0.04	0.95	0.07
10:102385430	HIF1AN	rs17094222	C	0.4511	-0.11	1.02	0.12
16:3567359	NLRC3	rs758747	T	0.4408	-0.08	0.96	0.09
14:29584863	PRKD1	rs11847697	T	0.4360	-0.64	1.51	0.43
14:24998019	STXBP6	rs10132280	C	0.4307	-0.06	0.92	0.09
19:50894012	QPCTL	rs2287019	C	0.4158	-0.15	0.98	0.15
11:27641093	BDNF	rs11030104	A	0.4068	-0.15	0.97	0.16
16:28240912	SBK1	rs2650492	A	0.3429	-0.14	0.82	0.16
17:1951886	SMG6	rs9914578	G	0.3256	-0.24	0.89	0.26
4:145878514	HHIP	rs11727676	T	0.2787	-0.52	1.08	0.49
19:50087459	TOMM40	rs2075650	A	0.2444	-0.38	0.87	0.44
5:75050998	POC5	rs2112347	T	0.2202	-0.24	0.68	0.35
8:76969685	HNF4G	rs17405819	T	0.2170	-0.27	0.71	0.39
17:76230166	RPTOR	rs12940622	G	0.2127	-0.24	0.67	0.36
9:28404339	LINGO2	rs10968576	G	0.2085	-0.27	0.69	0.39
2:62906552	EHBP1	rs11688816	G	0.2065	-0.25	0.66	0.37
11:47607569	MTCH2	rs3817334	T	0.1785	-0.29	0.64	0.45
16:28796987	ATP2A1	rs3888190	A	0.1740	-0.29	0.63	0.46
9:119418304	TLR4	rs1928295	T	0.1721	-0.29	0.63	0.46
19:18315825	PGPEP1	rs17724992	A	0.1704	-0.35	0.69	0.52
1:176156103	SEC16B	rs543874	G	0.1693	-0.41	0.75	0.57
12:48533735	BCDIN3D	rs7138803	A	0.1565	-0.30	0.62	0.51
7:95007450	ASB4	rs6465468	T	0.1528	-0.33	0.63	0.53
18:55034299	GRP	rs7243357	T	0.1423	-0.47	0.76	0.65
14:78969207	NRXN3	rs7141420	T	0.1330	-0.32	0.58	0.56
16:52361075	FTO	rs1558902	A	0.1288	-0.32	0.58	0.58
1:96696685	PTBP2	rs11165643	T	0.1244	-0.33	0.58	0.59
10:114748339	TCF7L2	rs7903146	C	0.0987	-0.40	0.60	0.70
16:47620091	CBLN1	rs2080454	C	0.0620	-0.41	0.53	0.80
2:219057996	USP37	rs492400	C	0.0511	-0.41	0.52	0.83
10:87400884	GRID1	rs7899106	G	0.0367	-0.99	1.07	0.94
6:137717234	IFNGR1	rs13201877	G	0.0337	-0.59	0.66	0.92
4:44877284	GNPDA2	rs10938397	G	0.0282	-0.42	0.48	0.90
2:142759755	LRP1B	rs2121279	T	0.0262	-0.62	0.67	0.94

9:128500735	LMX1B	rs10733682	A	0.0251	-0.42	0.48	0.91
5:153518086	GALNT10	rs7715256	G	0.0107	-0.45	0.48	0.96
3:25081441	RARB	rs6804842	G	0.0098	-0.45	0.47	0.97
21:39213610	ETS2	rs2836754	C	0.0083	-0.46	0.47	0.97
7:76446079	PMS2L11	rs2245368	C	0.0037	-0.60	0.61	0.99
2:25003800	ADCY3	rs10182181	G	0.0031	-0.45	0.46	0.99
3:81874802	GBE1	rs3849570	A	-0.0047	-0.47	0.46	0.98
13:53000207	OLFM4	rs12429545	A	-0.0058	-0.71	0.70	0.99
11:8630515	TRIM66	rs4256980	G	-0.0207	-0.49	0.45	0.93
2:181259207	UBE2E3	rs1528435	T	-0.0287	-0.50	0.44	0.90
3:61211502	FHIT	rs2365389	C	-0.0460	-0.50	0.41	0.84
19:52260843	ZC3H4	rs3810291	A	-0.0514	-0.53	0.42	0.83
7:75001105	HIP1	rs1167827	G	-0.0588	-0.52	0.40	0.80
9:15624326	C9orf93	rs4740619	T	-0.0615	-0.52	0.40	0.79
6:109084356	FOXO3	rs9400239	C	-0.0691	-0.56	0.42	0.78
3:187306698	ETVM	rs1516725	C	-0.0766	-0.74	0.58	0.82
1:78219349	FUBP1	rs12401738	A	-0.0771	-0.55	0.39	0.75
18:19358886	C18orf8	rs1808579	C	-0.0859	-0.54	0.37	0.71
7:93568420	CALCR	rs9641123 †	C	-0.0917	-0.60	0.41	0.72
13:78478920	MIR548A2	rs1441264	A	-0.0998	-0.56	0.37	0.67
2:226801046	LOC646736	rs2176040	A	-0.1026	-0.57	0.36	0.66
1:7477478	FPGT-TNNI3K	rs12566985	G	-0.1040	-0.57	0.36	0.66
16:29922838	INO80E	rs4787491	G	-0.1110	-0.56	0.34	0.63
15:65864222	MAP2K5	rs16951275	T	-0.1274	-0.66	0.41	0.64
11:114527614	CADM1	rs12286929	G	-0.1291	-0.58	0.32	0.58
6:40456631	TDRG1	rs2033529	G	-0.1365	-0.65	0.38	0.60
16:31037396	KAT8	rs9925964	A	-0.1480	-0.62	0.32	0.54
16:19842890	GPRC5B	rs12446632	G	-0.1560	-0.79	0.48	0.63
9:110972163	EPB41L4B	rs6477694	C	-0.1661	-0.63	0.29	0.48
11:43820854	HSD17B12	rs2176598	T	-0.1746	-0.70	0.35	0.51
3:85890280	CADM2	rs13078960	G	-0.1839	-0.76	0.39	0.53
13:65103705	MIR548X2	rs9540493	A	-0.1901	-0.64	0.26	0.41
2:59159129	LINC01122	rs1016287	T	-0.2020	-0.71	0.31	0.44
1:200050910	NAV1	rs2820292	C	-0.2066	-0.66	0.25	0.37
17:5223976	RABEP1	rs1000940	G	-0.2118	-0.71	0.28	0.40
2:207963763	CREB1	rs17203016	G	-0.2123	-0.77	0.35	0.46
2:26782315	KCNK3	rs11126666	A	-0.2389	-0.74	0.26	0.35
6:34671142	C6orf106	rs205262	G	-0.2469	-0.75	0.25	0.33
13:26915782	MTIF3	rs9581855 †	A	-0.2565	-0.86	0.35	0.40
6:50877777	TFAP2B	rs2207139	G	-0.2757	-0.86	0.31	0.36
1:47457264	TAL1	rs977747	T	-0.2793	-0.76	0.20	0.25
4:77315142	SCARB2	rs17001561 †	A	-0.2894	-0.94	0.36	0.38

15:70881044	LOC100287559	rs7164727	T	-0.3013	-0.79	0.19	0.23
1:109956211	GNAT2	rs17024393	C	-0.3038	-1.48	0.87	0.61
2:622348	TMEM18	rs13021737	G	-0.3150	-0.94	0.31	0.33
18:38401669	LOC284260	rs7239883	G	-0.3253	-0.79	0.14	0.17
20:50521269	ZFP64	rs6091540	C	-0.3280	-0.85	0.19	0.22
14:28806589	PRKD1	rs12885454	C	-0.3290	-0.80	0.14	0.17
1:72523773	NEGR1	rs3101336	C	-0.3713	-0.85	0.10	0.13
15:49535902	DMXL2	rs3736485	A	-0.3808	-0.83	0.07	0.10
6:162953340	PARK2	rs13191362	A	-0.3954	-1.16	0.37	0.31
8:85242264	RALYL	rs2033732	C	-0.4045	-0.92	0.11	0.12
1:49362434	AGBL4	rs657452	A	-0.4172	-0.88	0.04	0.08
2:164275935	FIGN	rs1460676	C	-0.4323	-1.03	0.17	0.16
3:141587171	RASA2	rs2035935 †	G	-0.5111	-1.40	0.38	0.26
2:213121476	ERBB4	rs7599312	G	-0.5464	-1.05	-0.04	0.03
10:104859028	NT5C2	rs11191560	C	-0.5638	-1.31	0.18	0.14
6:120227364	LOC285762	rs9374842	T	-0.5899	-1.11	-0.07	0.03
8:81538012	ZBTB10	rs16907751	C	-0.6183	-1.33	0.09	0.09
1:50332407	ELAVL4	rs11583200	C	-0.6562	-1.11	-0.20	0.01
12:121347850	CLIP1	rs11057405	G	-0.8565	-1.58	-0.13	0.02

*Position of build 36, (LD r^2>0.9); † proxy SNPs (rs2035935 as a proxy for rs16851483, rs17001561 as a proxy for rs17001654 and rs9581855 as a proxy for rs12016871).

Table s-16 Age- and sex-adjusted effects and corresponding 95% confidence interval (95% CI) of the interaction between each body mass index (BMI) associated single nucleotide polymorphism (SNP) and alcohol consumption [Alc; per 100g/week] in separate linear regression models, sorted by ascending effect size estimates.

Chr:Position*	Locus	SNP	Risk Allele	$ß_{SNPxAlc}$	95 % CI		*p*
					Lower	Upper	
3:141587171	RASA2	rs2035935 †	G	-0.3314	-0.71	0.05	0.09
6:50877777	TFAP2B	rs2207139	G	-0.2215	-0.46	0.01	0.06
18:38401669	LOC284260	rs7239883	G	-0.2158	-0.40	-0.03	0.02
7:76446079	PMS2L11	rs2245368	C	-0.2070	-0.46	0.05	0.12
3:85890280	CADM2	rs13078960	G	-0.2038	-0.45	0.04	0.10
17:76230166	RPTOR	rs12940622	G	-0.1878	-0.38	0.01	0.06
19:39001372	KCTD15	rs29941	G	-0.1823	-0.38	0.01	0.07
9:28404339	LINGO2	rs10968576	G	-0.1627	-0.36	0.04	0.11
16:28240912	SBK1	rs2650492	A	-0.1391	-0.34	0.06	0.18
1:72523773	NEGR1	rs3101336	C	-0.1289	-0.32	0.06	0.19
8:85242264	RALYL	rs2033732	C	-0.1236	-0.32	0.08	0.23
16:52361075	FTO	rs1558902	A	-0.1216	-0.32	0.08	0.24
6:40456631	TDRG1	rs2033529	G	-0.1183	-0.33	0.09	0.28
13:53000207	OLFM4	rs12429545	A	-0.1152	-0.42	0.19	0.45
19:50087459	TOMM40	rs2075650	A	-0.1125	-0.38	0.15	0.41
14:24998019	STXBP6	rs10132280	C	-0.1100	-0.32	0.10	0.31
2:207963763	CREB1	rs17203016	G	-0.1067	-0.33	0.12	0.35
1:47457264	TAL1	rs977747	T	-0.1030	-0.29	0.08	0.28
11:47607569	MTCH2	rs3817334	T	-0.0979	-0.29	0.09	0.31
2:213121476	ERBB4	rs7599312	G	-0.0965	-0.31	0.12	0.38
5:153518086	GALNT10	rs7715256	G	-0.0950	-0.28	0.09	0.32
18:55034299	GRP	rs7243357	T	-0.0880	-0.33	0.15	0.47
14:28806589	PRKD1	rs12885454	C	-0.0878	-0.28	0.11	0.38
4:103407732	SLC39A8	rs13107325	T	-0.0852	-0.49	0.32	0.68
4:77315142	SCARB2	rs17001654†	A	-0.0760	-0.35	0.20	0.59
14:78969207	NRXN3	rs7141420	T	-0.0743	-0.26	0.11	0.43
16:3567359	NLRC3	rs758747	T	-0.0684	-0.28	0.14	0.53
2:62906552	EHBP1	rs11688816	G	-0.0624	-0.26	0.14	0.54
15:65864222	MAP2K5	rs16951275	T	-0.0623	-0.29	0.16	0.59
6:162953340	PARK2	rs13191362	A	-0.0617	-0.36	0.23	0.68
12:121347850	CLIP1	rs11057405	G	-0.0602	-0.37	0.25	0.70
10:87400884	GRID1	rs7899106	G	-0.0587	-0.55	0.43	0.82
16:28796987	ATP2A1	rs3888190	A	-0.0580	-0.25	0.13	0.55
1:78219349	FUBP1	rs12401738	A	-0.0560	-0.25	0.14	0.57
14:29584863	PRKD1	rs11847697	T	-0.0473	-0.72	0.62	0.89

2:59159129	LINC01122	rs1016287	T	-0.0416	-0.25	0.17	0.70
13:65103705	MIR548X2	rs9540493	A	-0.0392	-0.22	0.15	0.68
2:26782315	KCNK3	rs11126666	A	-0.0383	-0.24	0.16	0.71
17:5223976	RABEP1	rs1000940	G	-0.0339	-0.24	0.18	0.75
10:104859028	NT5C2	rs11191560	C	-0.0318	-0.34	0.28	0.84
2:142759755	LRP1B	rs2121279	T	-0.0317	-0.29	0.23	0.81
3:25081441	RARB	rs6804842	G	-0.0278	-0.22	0.17	0.78
8:76969685	HNF4G	rs17405819	T	-0.0190	-0.21	0.17	0.85
11:8630515	TRIM66	rs4256980	G	-0.0153	-0.20	0.17	0.87
5:75050998	POC5	rs2112347	T	-0.0139	-0.21	0.18	0.89
2:181259207	UBE2E3	rs1528435	T	-0.0119	-0.21	0.18	0.90
6:109084356	FOXO3	rs9400239	C	-0.0107	-0.22	0.19	0.92
3:61211502	FHIT	rs2365389	C	-0.0026	-0.19	0.18	0.98
2:226801046	LOC646736	rs2176040	A	0.0002	-0.18	0.19	1.00
7:75001105	HIP1	rs1167827	G	0.0026	-0.19	0.19	0.98
13:78478920	MIR548A2	rs1441264	A	0.0028	-0.20	0.20	0.98
1:7477478	FPGT-TNNI3K	rs12566985	G	0.0084	-0.18	0.19	0.93
7:93568420	CALCR	rs9641123†	C	0.0091	-0.20	0.22	0.93
10:114748339	TCF7L2	rs7903146	C	0.0119	-0.20	0.22	0.91
19:52260843	ZC3H4	rs3810291	A	0.0175	-0.18	0.21	0.86
11:43820854	HSD17B12	rs2176598	T	0.0281	-0.18	0.23	0.79
18:19358886	C18orf8	rs1808579	C	0.0282	-0.15	0.21	0.76
19:18315825	PGPEP1	rs17724992	A	0.0293	-0.18	0.24	0.78
10:102385430	HIF1AN	rs17094222	C	0.0314	-0.22	0.28	0.80
3:187306698	ETVM	rs1516725	C	0.0346	-0.26	0.33	0.82
1:49362434	AGBL4	rs657452	A	0.0428	-0.15	0.23	0.66
16:47620091	CBLN1	rs2080454	C	0.0436	-0.15	0.24	0.66
6:120227364	LOC285762	rs9374842	T	0.0442	-0.16	0.25	0.68
1:50332407	ELAVL4	rs11583200	C	0.0593	-0.13	0.24	0.53
6:34671142	C6orf106	rs205262	G	0.0606	-0.17	0.29	0.60
9:110972163	EPB41L4B	rs6477694	C	0.0628	-0.12	0.25	0.50
1:96696685	PTBP2	rs11165643	T	0.0681	-0.13	0.26	0.49
6:137717234	IFNGR1	rs13201877	G	0.0691	-0.20	0.34	0.62
1:176156103	SEC16B	rs543874	G	0.0702	-0.15	0.30	0.54
1:200050910	NAV1	rs2820292	C	0.0755	-0.11	0.26	0.41
17:1951886	SMG6	rs9914578	G	0.0803	-0.17	0.33	0.53
12:48533735	BCDIN3D	rs7138803	A	0.0805	-0.12	0.28	0.43
11:27641093	BDNF	rs11030104	A	0.0826	-0.14	0.31	0.47
4:145878514	HHIP	rs11727676	T	0.0995	-0.22	0.42	0.54
2:622348	TMEM18	rs13021737	G	0.1055	-0.16	0.37	0.44

16:31037396	KAT8	rs9925964	A	0.1158	-0.07	0.30	0.23
20:50521269	ZFP64	rs6091540	C	0.1191	-0.09	0.33	0.26
16:29922838	INO80E	rs4787491	G	0.1222	-0.06	0.30	0.19
7:95007450	ASB4	rs6465468	T	0.1236	-0.07	0.32	0.22
15:49535902	DMXL2	rs3736485	A	0.1246	-0.06	0.31	0.18
4:44877284	GNPDA2	rs10938397	G	0.1282	-0.06	0.31	0.18
2:219057996	USP37	rs492400	C	0.1311	-0.07	0.33	0.20
9:128500735	LMX1B	rs10733682	A	0.1333	-0.06	0.32	0.17
19:50894012	QPCTL	rs2287019	C	0.1345	-0.09	0.36	0.24
2:164275935	FIGN	rs1460676	C	0.1349	-0.13	0.40	0.32
21:39213610	ETS2	rs2836754	C	0.1361	-0.06	0.33	0.17
3:81874802	GBE1	rs3849570	A	0.1445	-0.05	0.34	0.14
2:25003800	ADCY3	rs10182181	G	0.1458	-0.04	0.33	0.12
8:81538012	ZBTB10	rs16907751	C	0.1467	-0.14	0.44	0.32
9:15624326	C9orf93	rs4740619	T	0.1577	-0.02	0.34	0.09
15:70881044	LOC100287559	rs7164727	T	0.1636	-0.03	0.36	0.10
18:55980115	MC4R	rs6567160	C	0.2105	0.00	0.42	0.05
9:119418304	TLR4	rs1928295	T	0.2180	0.03	0.40	0.02
11:114527614	CADM1	rs12286929	G	0.2562	0.06	0.45	0.01
13:26915782	MTIF3	rs12016871†	A	0.3062	0.05	0.56	0.02
16:19842890	GPRC5B	rs12446632	G	0.3417	0.06	0.62	0.02
1:109956211	GNAT2	rs17024393	C	0.4159	-0.07	0.90	0.09

*Position of build 36, (LD r^2>0.9); † proxy SNPs (rs2035935 as a proxy for rs16851483, rs17001561 as a proxy for rs17001654 and rs9581855 as a proxy for rs12016871).

8.2 List of abbreviations

A	Adenine
Alc	Alcohol
ß	Beta-estimate
BMI	Body mass index
bp	Base pair
C	Cytosine
CI	Confidence interval
CLIP1	CAP-Gly domain containing linker protein 1
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
€	Euro (currency unit)
EDTA	Ethylenediamine tetraacetic acid
FTO	Fat mass and obesity associated
g	Gram (measuring unit)
G	Guanine
GxE	Gene by environment interaction
GxSES	Gene by socioeconomic status interaction
GIANT	Genetic Investigation of Anthropometric Traits consortium
GRS	Genetic risk score
GRSxAlc	Genetic risk score by alcohol consumption interaction
GRSxPA	Genetic risk score by physical activity interaction
GRSxS	Genetic risk score by smoking interaction
GRSxSES	Genetic risk score by socioeconomic status interaction
GWAS	Genome-wide association studies
HNR	Heinz Nixdorf Recall Study
HSD17B12	Hydroxysteroid 17-beta dehydrogenase 12

HWE	Hardy-Weinberg equilibrium
IQR	Interquartile range
ISCED	International Standard Classification of Education
KCTD15	Potassium channel tetramerization domain containing 15
kg	Kilogram (measuring unit)
LD	Linkage disequilibrium
m	Meter (measuring unit)
m^2	Square meter (measuring unit)
MAF	Minor allele frequency
MALDI-TOF	Matrix-assisted laser desorption ionization-time of flight
MC4R	Melanocortin 4 receptor gene
MIR548X2	MicroRNA 548x-2
NCBI	National Center for Biotechnology Information
OECD	Organization for Economic Co-operation and Development
PA	Physical activity
Recall	Risk factors, evaluation of coronary calcium and lifestyle
S	Smoking
SD	Standard deviation
SES	Socioeconomic status
SNP	Single nucleotide polymorphisms
SNAP	SNP Annotation and Proxy Search
STXBP6	Syntaxin binding protein 6
T	Thymine
wGRS	Weighted genetic risk score
WHO	World Health Organization

8.3 List of tables

Supplementary tables

8.4 List of figures

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10 Curriculum Vitae

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.