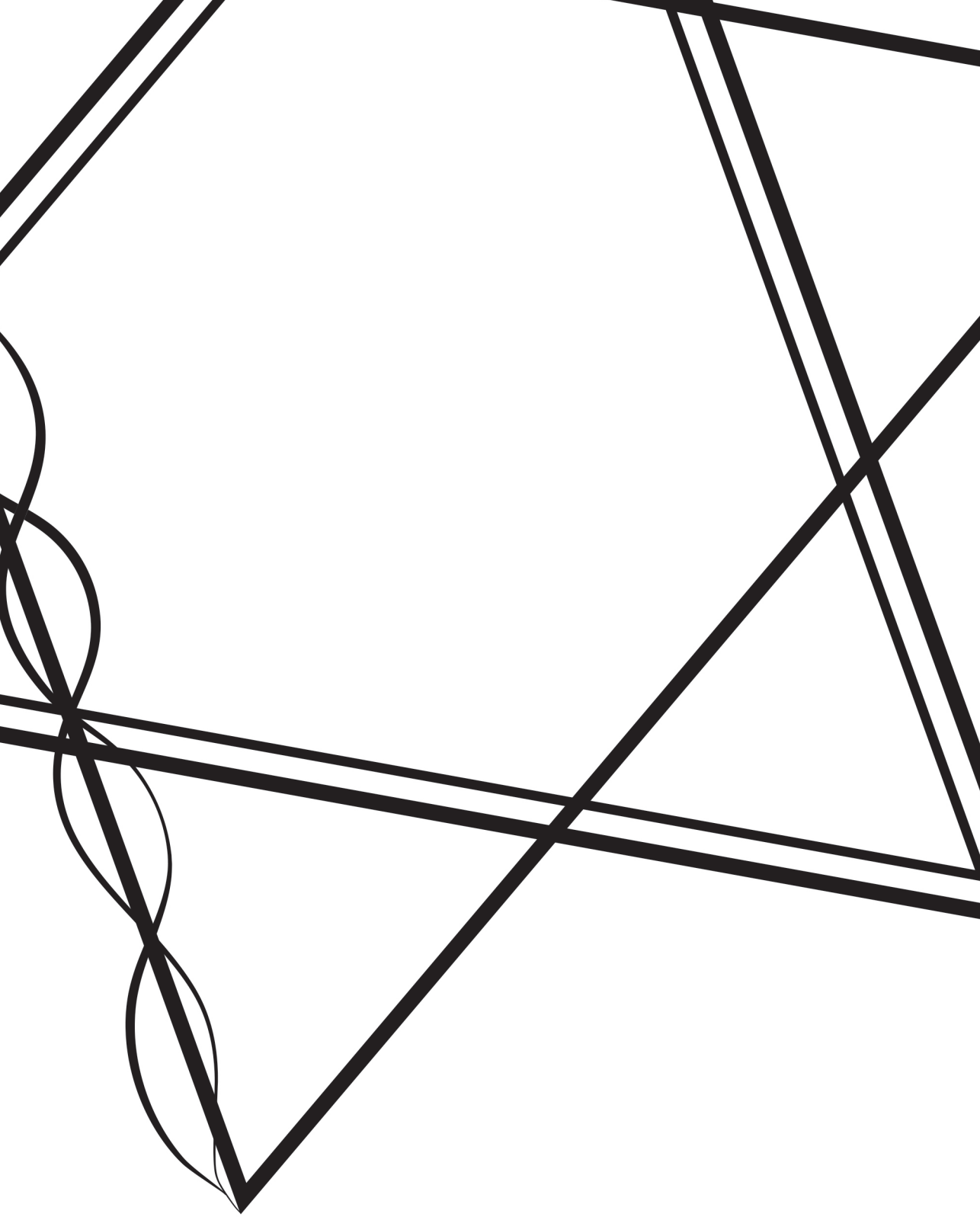
Genetic and environmental determinants of cardiometabolic health

Bos, M.M.



CHAPTER 1

General introduction and thesis outline

Maxime M Bos

INTRODUCTION

The science of medicine is one of the oldest areas of science and has been proven to be very successful. Because of better hygiene, improved treatment options and vaccinations, numerous early deaths have been prevented, thereby greatly increasing our overall survival. As a consequence, our life expectancy has greatly increased. However, because of this increased life expectancy, the world's population is ageing and virtually every country experiences a growth in the proportion of older individuals in their population. In line, the prevalence of age-related diseases has greatly increased and is expected to increase as the population keeps on aging[1]. Although improved cardiovascular risk management (serum cholesterol, blood pressure, smoking, diet) has reduced early deaths due to cardiovascular disease (CVD), CVD remains the leading cause of death of older adults in many developed as well as developing countries and accounted for a total of 17.9 million deaths in 2015[2, 3]. Moreover, a steep increase is seen in the prevalence of type 2 diabetes mellitus. The global prevalence of diabetes mellitus has risen from 108 million individuals (4.7%) in 1980 to 422 million individuals (8.5%) in 2014[4]. Diabetes is one of the major causes for cardiovascular diseases, stroke and kidney failure. Cardiometabolic health and cardiometabolic diseases are terms to describe cardiovascular and metabolic diseases, such as type 2 diabetes mellitus and the metabolic syndrome. Given the public health significance of understanding cardiometabolic diseases, research focusing on a better understanding of causal determinants is of importance.

Obesity is a key risk factor for cardiometabolic diseases. In a few decades, the prevalence of obesity has doubled and this number is expected to further increase. Obesity is just one of the many causes that may lead to cardiometabolic disorders. Many other factors, including age, sex, hormonal-, genetic- and environmental factors jointly determine the individual risk of developing cardiometabolic disorders[5]. For example, non-modifiable factors such as family history and ethnicity all determine metabolic health. Next to these non-modifiable risk factors, modifiable factors such as smoking, physical activity and nutrition all have their own effect on metabolic health as well. Moreover, nearly all diseases result from a complex interaction between an individual's genetic make-up and the environmental factors that one is exposed to. Given the public health significance of understanding cardiometabolic diseases, research focusing on a better understanding of causal determinants is pivotal. Moreover, a better understanding of the interrelations of these risk factors may improve research focused on preventive and treatment strategies for cardiometabolic disorders. Therefore, the aim of this thesis is to study the interplay of non-modifiable (genetic) risk and modifiable lifestyle factors (e.g. sleep, nutrition, physical activity) on cardiometabolic health. In this thesis, several

possible and established risk factors for cardiometabolic disorders will be studied and the causal effects of these factors will be explored. This thesis thereby aims to contribute to a better understanding of determinants of cardiometabolic health in order to decrease the burden of cardiometabolic disorders and age-related diseases on the patient and the society.

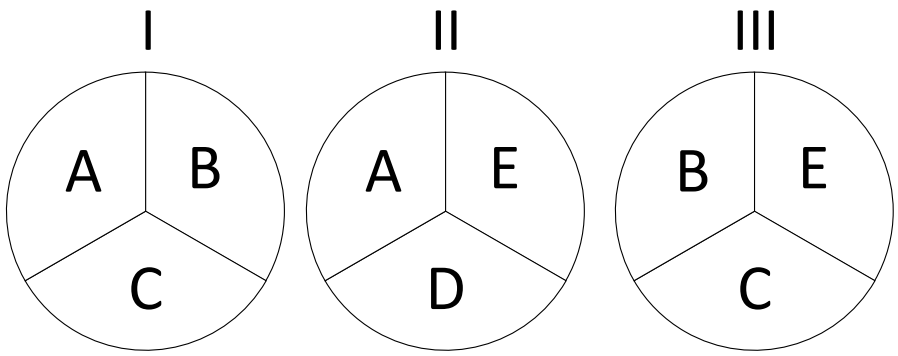


Figure 1. *The causal pie model:* Component causes A-E add up to the sufficient causes I-III. Every sufficient cause consists of different component causes. If and only if all the component causes that constitute the causal pie of a sufficient cause are present, does the sufficient cause exist and does the outcome occur. Hence, the effect of a component cause depends on the presence of its complementary component causes, that is, its complementary set. I, II, and III can be sufficient causes for the same outcome, or for different outcomes, in which case the outcomes are correlated through the component causes. Adapted from Wensink (2014)[6].

Epidemiology and the causal pie model

The study of epidemiology is mainly focussed on determining causes of specific health outcomes and diseases in defined populations. Epidemiology is the cornerstone of public health and is important in shaping policy decisions and evidence-based practices. This field is aimed at identifying risk factors for disease and targets for preventive or curative healthcare. In order to have a better grasp of the idea of causality, the 'causal pie model' of Rothman is a general model widely used in epidemiology[6]. To cite Rothman: "the lights at home shine because they each have a light bulb, there is wire to the light bulbs, the switches are on, there is a power grid, and there is a power source. Take any of these factors away, and there is no light: The system contains 500% causality, for all five factors are 100% causative for the shining of the light. There is no limit to the sum of causes for some outcome"[7]. In **Figure 1**, the causal pie model of Rothman is depicted. In this model, a sufficient cause is a constellation of component causes. The combination of these component causes reflects the causal pie, which leads to a specific outcome. Each component cause can be part of more than one causal pie. In

order for the outcome to occur, all the components that make up the causal pie have to be present. Therefore, the effect of a component cause depends on the presence of the other component causes, which are called complementary component causes. In the case of cardiometabolic health, a sufficient cause can be something as the occurrence of a cardiovascular event. Several component causes make up the causal pie for this outcome, for example, presence of obesity and a high cholesterol level. Moreover, these component causes can be part of other causal pies, such as one for type 2 diabetes mellitus onset (e.g. obesity). In the light of the causal pie model, it is of interest to study which component causes make up a causal pie for a specific cardiometabolic health related outcome.

Lifestyle factors

Lifestyle is a major contributor to risk for the development of cardiometabolic diseases. Besides smoking, the most well-known and established risk factors for cardiometabolic disease are excess caloric intake due to overeating, and a lack of physical activity[5]. As a result of this disbalance between the intake of energy and the expenditure of energy, we eventually will gain weight[5, 8]. During the past decade, sleep has emerged as another lifestyle factor that may contribute to the risk of cardiometabolic disease onset. Sleep is an essential homeostatistically regulated state in which there is decreased activity and alertness[9]. Sleep, or a sleep-like state, is observed across different animal species[9, 10]. Despite extensive studies, the exact mechanistic aspects of sleep are not very well understood. Even less well understood is the association of different aspects of sleep with cardiometabolic health. In several studies, it has been observed that both short and long total sleep duration were associated with a higher risk of obesity, insulin resistance, and diabetes mellitus [11-14]. However, other studies reported only short sleep duration and not long sleep duration to be associated with a higher risk of obesity and metabolic syndrome [15, 16]. Therefore, further study in the field of sleep and cardiometabolic diseases is warranted. Furthermore, insights in the potential biological mechanisms linking disturbances in habitual sleep and cardiometabolic outcomes are warranted to promote further research in prevention and treatment strategies in individuals with disturbed sleep patterns.

Thyroid hormone metabolism

Next to lifestyle factors and genetic predisposition, it is increasingly recognized that endocrine disorders affect cardiometabolic health. Among these are (subclinical) hypothyroidism and hyperthyroidism, which are characterised by a deficit or excess of thyroid hormones. Thyroid hormones act on nearly every cell in the body and thereby exert a wide range of functions. The concentration of thyroid hormones in the circulation is tightly regulated by the hypothalamic pituitary-thyroid axis. Thyrotropin-releasing hormone, secreted by the hypothalamus, regulates synthesis and release of thyroid-

stimulating hormone (TSH) from the pituitary gland, which stimulates the production and secretion of the thyroid hormones by the thyroid gland. Via a classical feedback loop, thyroid hormones inhibit the production of hypothalamic thyrotropin-releasing hormone and pituitary TSH. In target tissues, type 1 and 2 deiodinases convert the prohormone thyroxine into the active hormone triiodothyronine, while type 3 deiodinase converts thyroxine into inactive reverse triiodothyronine[17, 18]. Increasing evidence suggests the existence of an association between thyroid function and cardiometabolic diseases, including atrial and ventricular arrhythmias, atherosclerotic vascular disease, dyslipidemia, and heart failure. In addition, several studies have reported that subclinical hypothyroidism is related to insulin resistance and type 2 diabetes mellitus[19]. However, evidence regarding the causal effect of thyroid hormones on cardiometabolic diseases is lacking.

Genetic epidemiology

The field of genetic epidemiology focusses on the role of genetic factors, and the interplay with environmental factors, in determining health and disease status in populations. Genetic epidemiology thereby seeks to derive a statistical and quantitative analysis on how genetics work in large populations. Genome-wide association studies have been performed to discover genetic variations, single nucleotide polymorphisms (SNPs), without a predefined hypothesis, that are associated with disease traits. A considerable part of the risk of cardiometabolic diseases has a genetic basis. In relation to cardiometabolic disease and human longevity, the top associated SNPs are in the *APOE* gene. Candidate gene studies and GWAS found that genetic variation in *APOE* is robustly associated with multiple cardiometabolic diseases and age-related phenotypes[20, 21]. Apolipoprotein E (ApoE) is an apolipoprotein that plays an important role in triglyceride and cholesterol metabolism. Especially the ApoE ε4 isoform has been associated with mortality, Alzheimer's disease and cardiovascular disease, as compared to the 'neutral' ApoE ε3 isoform[22]. There are, however, large differences in the deleterious effects of the ApoE ε4 isoform between ancestries and populations. One explanation may be the differences in environmental and lifestyle factors between these populations. Nearly all diseases result from a complex interaction between an individual's genetic make-up and the environmental factors that one is exposed to. However, differences in the response to a certain environmental factor may occur in the presence of different genotypes. As a result, some individuals may possess a low risk for developing a certain disease though the exposure to an environmental factor, while other may be more vulnerable. An example of a so called gene-environment interaction, is the higher incidence of skin cancer among fair-skinned individuals as compared to darker skinned individuals as a result to sunlight exposure. In short, two different genotypes respond to an environmental factor in a different way. In relation to the causal pie model, it can therefore be stated that the size of a specific component is not fixed and can differ based on the presence of other component causes.

In the case of a gene-environment interaction, for example, the size of a component (e.g. genetic) can alter based on the presence of a certain environmental factor thereby more rapidly filling the causal pie. In this respect, poor nutrition and physical inactivity are two important lifestyle factors that have been associated with increased risks for Alzheimer's disease and cardiometabolic diseases. It has been hypothesized, that these lifestyle factors may interact with genetic variation in the *APOE* gene thereby altering the risk for disease onset. Therefore, studies focussing on genetic variation in *APOE* and the interaction with lifestyle factors on the risk of cardiometabolic diseases are of importance.

Causal inference and Mendelian Randomization

In general, the study of epidemiology is viewed as a collection of statistical tools used to elucidate associations of exposures to health and disease outcomes. However, a deeper understanding of this science is that of discovering of causal relationships between exposures and outcomes. Therefore, a key term is causal inference. An association or correlation between two variables may be necessary, but is not sufficient for causal inference, notably that one variable causes the other. If a causal variable can be identified and controlled, the disease outcome can be avoided. One method used to ascertain causality of observational associations, free of confounding and reverse causality, is Mendelian randomization [23, 24](**Figure 2**). Mendelian randomization is based on Mendel's second law, the law of independent assortment, which states that germline genetic variation is subject to the random allocation of alleles at conception. This method uses genetic variants, SNPs, as instrumental variable for the exposure of interest[25]. This instrumental variable is associated with the exposure, but not with the outcome of interest, except through its association with the exposure. Since the association between the genetic variants and the clinical outcome of interest are generally independent of environmental or behavioural factors, these SNPs can be used to avoid possible confounding or reverse causality and thereby enable to study the causal effect of an exposure of interest on an outcome.

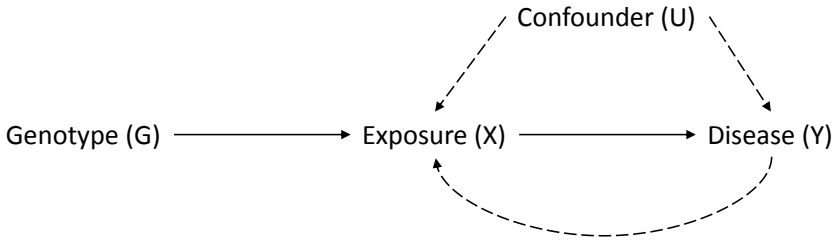


Figure 2. *The design of Mendelian randomization:* the genotype is associated with the exposure, the genotype is independent of confounders and the genotype is associated with the outcome, but only through the exposure of interest.

OUTLINE OF THIS THESIS

In this thesis, we will focus on the interplay between non-modifiable factors (genetics) and modifiable lifestyle factors (e.g. sleep, nutrition, physical activity) with cardiometabolic health. In **Chapter 2**, we aimed to identify early metabolic biomarkers that associate with insulin resistance in non-diabetic individuals and to what extend those biomarkers were associated with diabetes mellitus. This study has been performed in the Leiden Longevity Study, a study of long-lived families of Caucasian origin and the findings were validated in the Netherlands Epidemiology of Obesity (NEO) study. The NEO study is a population-based cohort study in overweight and obese middle-aged individuals from the Leiden region in The Netherlands. Next, we will focus on lifestyle factors. Since sleep is an important lifestyle factor in regard to cardiometabolic health, the following three chapters will be focused around sleep. The first two studies of this section have been performed in the NEO study. First, we will address the association between sleep duration and sleep quality with blood lipid levels and hepatic lipid content in **Chapter 3.1**. In **Chapter 3.2**, the focus will be on sleep duration and sleep quality with insulin resistance. From this chapter on, we will also focus on the genetic aspects of cardiometabolic health, since this study will also include a part that assesses the association between genetically determined sleep duration and insulin resistance. **Chapter 3.3** will focus on the identification of novel lipid loci if we take into account interaction with sleep duration in a large multi-ancestry analysis. This study is part of the CHARGE consortium. The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium was formed to facilitate genome-wide association study meta-analyses and replication opportunities among multiple large and well-phenotyped longitudinal cohort studies. We will move from sleep duration to food intake and physical activity in **Chapter 4.1**. This chapter is a review in which we discuss the effect of physical activity, oily fish intake and omega-3 fatty acid intake on the risk of diseases associated with genetic variation in the *APOE* gene. Next, we will study whether the risk of cardiovascular disease indeed may be modified by physical activity and food intake in a large cohort study. This is done in **Chapter 4.2**, in which we will describe the associations between genetic variation in *APOE* and lifestyle factors in the UK Biobank. The UK Biobank is a large long-term biobank study with deep genetic, physical and health data collected on ~500,000 individuals in the United Kingdom. In this study, we aimed to investigate the presence of a gene-lifestyle interaction in relation to coronary artery disease incidence. The final two chapters of this thesis, **Chapters 5.1** and **5.2**, will focus on the association between alterations in hormone metabolism and cardiometabolic health. Specifically, we will assess the association between genetically determined thyroid hormone levels and the risk of type 2 diabetes and measures of glucose

homeostasis using Mendelian Randomization in **Chapter 5.1**. In **Chapter 5.2**, the causal of effect of thyroid hormone status on diabetes mellitus and the effect of BMI will be studied. This study will be performed in the UK Biobank. In the last part of this thesis (**Chapter 6**), the study findings together with their implications for future research are discussed.

REFERENCES

1. Omran AR. The epidemiologic transition. A theory of the epidemiology of population change. Milbank Mem Fund Q. 1971;49(4):509-38.
2. Afshin A, Reitsma MB, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries. N Engl J Med. 2017;377(15):1496-7.
3. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.
4. Emerging Risk Factors C, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
5. Medicine Io. Genes, Behavior, and the Social Environment: Moving Beyond the Nature/Nurture Debate. Hernandez LM, Blazer DG, editors. Washington, DC: The National Academies Press; 2006. 384 p.
6. Wensink M, Westendorp RG, Baudisch A. The causal pie model: an epidemiological method applied to evolutionary biology and ecology. Ecol Evol. 2014;4(10):1924-30.
7. Rothman KJ. Causes. Am J Epidemiol. 1976;104(6):587-92.
8. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. Science. 1999;283(5399):212-4.
9. Zielinski MR, McKenna JT, McCarley RW. Functions and Mechanisms of Sleep. AIMS Neurosci. 2016;3(1):67-104.
10. Allada R, Siegel JM. Unearthing the phylogenetic roots of sleep. Curr Biol. 2008;18(15):R670-R9.
11. Wong PM, Manuck SB, DiNardo MM, Korytkowski M, Muldoon MF. Shorter sleep duration is associated with decreased insulin sensitivity in healthy white men. Sleep. 2015;38(2):223-31.
12. Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. Annals of the New York Academy of Sciences. 2014;1311:151-73.
13. Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep. 2008;31(5):619-26.
14. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33(2):414-20.
15. Wu Y, Zhai L, Zhang D. Sleep duration and obesity among adults: a meta-analysis of prospective studies. Sleep Med. 2014;15(12):1456-62.
16. Xi B, He D, Zhang M, Xue J, Zhou D. Short sleep duration predicts risk of metabolic syndrome: a systematic review and meta-analysis. Sleep Med Rev. 2014;18(4):293-7.
17. Bianco AC, Larsen PR. Cellular and structural biology of the deiodinases. Thyroid. 2005;15(8):777-86.
18. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002;23(1):38-89.
19. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol. 2009;160(5):785-90.

20. Deelen J, Beekman M, Uh HW, Broer L, Ayers KL, Tan Q, et al. Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. Hum Mol Genet. 2014;23(16):4420-32.
21. Pilling LC, Atkins JL, Bowman K, Jones SE, Tyrrell J, Beaumont RN, et al. Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. Aging (Albany NY). 2016;8(3):547-60.
22. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997;278(16):1349-56.
23. Katan MB. Apolipoprotein E isoforms, serum cholesterol, and cancer. Lancet. 1986;1(8479):507-8.
24. Trompet S, Jukema JW, Katan MB, Blauw GJ, Sattar N, Buckley B, et al. Apolipoprotein e genotype, plasma cholesterol, and cancer: a Mendelian randomization study. Am J Epidemiol. 2009;170(11):1415-21.
25. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med. 2008;27(8):1133-63.