



Universiteit
Leiden
The Netherlands

Associations between outdoor temperature and bright sunlight with metabolites in two population-based European cohorts

Maarse, B.C.E.; Loh, N.Y.; Karpe, F.; Rosendaal, F.R.; Heemst, D. van; Mook-Kanamori, D.O.; ... ; Noordam, R.

Citation

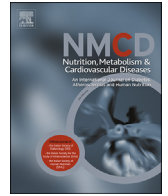
Maarse, B. C. E., Loh, N. Y., Karpe, F., Rosendaal, F. R., Heemst, D. van, Mook-Kanamori, D. O., ... Noordam, R. (2020). Associations between outdoor temperature and bright sunlight with metabolites in two population-based European cohorts. *Nutrition, Metabolism & Cardiovascular Diseases*, 30(12), 2252-2261. doi:10.1016/j.numecd.2020.07.030

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3184613>

Note: To cite this publication please use the final published version (if applicable).



Associations between outdoor temperature and bright sunlight with metabolites in two population-based European cohorts

Boukje C. Eveleens Maarse^a, Nellie Y. Loh^b, Fredrik Karpe^{b,c}, Frits R. Rosendaal^d, Diana van Heemst^e, Dennis O. Mook-Kanamori^d, Ko Willems van Dijk^{a,f}, Patrick C.N. Rensen^a, Sander Kooijman^{a,b}, Constantinos Christodoulides^{b,**,1}, Raymond Noordam^{e,*,1}

^a Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, the Netherlands

^b Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

^c NIHR Oxford Biomedical Research Centre, OUH Foundation Trust, Oxford, UK

^d Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

^e Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands

^f Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands

Received 14 March 2020; received in revised form 19 July 2020; accepted 20 July 2020

Handling Editor: A. Siani

Available online 28 July 2020

KEYWORDS

Cohort studies;
Epidemiology;
Lipoproteins;
Metabolomics;
Outdoor bright
sunlight;
Outdoor temperature

Abstract *Background and aims:* Outdoor temperature and bright sunlight may directly and/or indirectly modulate systemic metabolism. We assessed the associations between outdoor temperature and bright sunlight duration with metabolomics.

Methods and results: Cross-sectional analyses were undertaken in non-diabetic individuals from the Oxford BioBank (OBB; N = 6368; mean age 47.0 years, males 44%) and the Netherlands Epidemiology of Obesity (NEO; N = 5916; mean age 55.6 years, males 43%) study. Data on mean outdoor bright sunlight and temperature were collected from local weather stations in the week prior to blood sampling. Fasting serum levels of 148 metabolites, including 14 lipoprotein subclasses, were measured using NMR spectroscopy. Linear regression analyses were performed to assess the associations between mean outdoor temperature and bright sunlight duration with metabolomics adjusted for age, sex, body mass index, season and either outdoor temperature or bright sunlight. A higher mean outdoor temperature was associated with increased serum concentrations of lipoprotein (sub)particles (β (SE) = 0.064 (0.018) SD per 5 °C, $p = 5.03e^{-4}$) and certain amino acids such as phenylalanine (0.066 (0.016) SD, $p = 6.44e^{-05}$) and leucine (0.111 (0.018) SD, $p = 1.25e^{-09}$). In contrast, longer duration of bright sunlight was specifically associated with lower concentrations of very low-density lipoprotein (sub)particles (e.g., VLDL cholesterol (-0.024 (0.005) SD per 1-h bright sunlight, $p = 8.06e^{-6}$)). The direction of effects was generally consistent between the OBB and NEO, although effect sizes were generally larger in the OBB.

Conclusions: Increased bright sunlight duration is associated with an improved metabolic profile whilst higher outdoor temperature may adversely impact cardiometabolic health.

© 2020 The Italian Diabetes Society, the Italian Society for the Study of Atherosclerosis, the Italian Society of Human Nutrition and the Department of Clinical Medicine and Surgery, Federico II University. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

* Corresponding author. Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, the Netherlands. Fax: +31 0 71 526 6912.

** Corresponding author. Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford OX3 7LE, UK.

E-mail addresses: costas.christodoulides@ocdem.ox.ac.uk (C. Christodoulides), r.noordam@lumc.nl (R. Noordam).

¹ These are joint senior authors.

Introduction

Outdoor temperature and sunlight intensity and duration affect our daily activities and may consequently have an impact on metabolic health status. Human and animal studies have also highlighted that environmental temperature and sunlight exposure may directly impact systemic metabolism e.g. by modulating brown adipose tissue (BAT) activity and influencing circadian rhythms [1]. Consistent with these notions several epidemiological studies have identified associations between outdoor temperature and prevalence of both type 2 diabetes mellitus (T2D) and cardiovascular diseases [2–4]. For example, Blauw et al. showed that the incidence of diabetes was greater in U.S. states with a higher average annual temperature [4]. Similarly, by investigating the associations between outdoor weather conditions and metabolic traits in two European population-based cohorts, namely the Oxford BioBank (OBB) and the Netherlands Epidemiology of Obesity (NEO) study, we recently demonstrated that increased bright sunlight exposure was associated with a lower Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and reduced plasma triglyceride levels in apparently healthy subjects [5]. In contrast, no associations between mean outdoor temperature and glucose or lipid metabolism were detected in the same study. These results indicate that outdoor sunlight may be specifically associated with a more beneficial cardiometabolic risk profile, although further studies are necessary to confirm these findings and determine the biological mechanism(s) underpinning these associations.

Recently, high-throughput metabolite profiling has emerged as a powerful tool for the exploration of disease mechanisms and the identification of novel therapeutic targets [6–9], especially in the context of cardiometabolic disorders [10,11]. Based on our earlier study [5], we hypothesized that outdoor bright sunlight would be associated with a more favourable metabolite profile. In this study, we performed a cross-sectional analysis investigating the association between outdoor bright sunlight and environmental temperature with plasma levels of 148 lipid and metabolite species as determined by NMR spectroscopy in a combined sample of over 12,000 middle-aged population-based subjects, without pre-existing diabetes mellitus, from the OBB and NEO study cohorts.

Methods

Study design

The OBB is a population-based cohort of randomly selected healthy participants aged 30–50 years from Oxfordshire (UK). Individuals with a history of myocardial infarction, diabetes mellitus, heart failure, untreated malignancy, other ongoing systemic diseases or ongoing pregnancy were not eligible for study inclusion. Participants were included between 1999 and May 2015. The OBB cohort comprises 7185 individuals. A more detailed description of

the study recruitment criteria and population characteristics is reported elsewhere [12].

The NEO study is population-based prospective cohort study of men and women aged between 45 and 65 years with an oversampling of individuals with a self-reported BMI of 27 kg/m² or higher, living in the greater area of Leiden (in the West of the Netherlands). In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited in the study irrespective of their BMI, to allow for a reference distribution of BMI. Between September 2008 and September 2012, 6671 individuals were included in the study. Detailed information about the study design and data collection has been described previously [13].

In both cohorts, participants were invited for a detailed baseline assessment, conducted after an overnight fast, which included blood sampling and anthropometry. Both studies were approved by local ethics committees, and written informed consent was obtained from all study participants.

Study population

In the OBB, we excluded individuals with missing data on mean outdoor temperature and/or bright sunlight in the week preceding the centre visit, body composition, and fasting metabolomics (missing in 817 individuals). Consequently, data from 6368 individuals were used for the present analyses. From NEO, we excluded individuals with both treated and diagnosed diabetes, as well as subjects with a fasting glucose concentration above 7.0 mmol/L ($N = 749$) in order to have a uniform population as that of the OBB regarding glycaemic status. Additionally, we excluded participants who were nonfasting, or had missing data on mean outdoor temperature and/or bright sunlight in the week preceding the centre visit, body composition, and fasting metabolomics (missing in 6 individuals). As a result, a total of 5916 individuals were used for the analyses presented in this study.

Data collection on outdoor temperature and bright sunlight

Data on the mean temperature and hours of bright sunlight (defined as global radiation >120 W/m²) were collected from the weather station that was located closest located to either Oxfordshire or Leiden. Based on these data, we estimated the mean outdoor temperature and bright light over the week prior to the date of the blood sampling. For the OBB data were obtained from the Radcliffe Meteorological Station (Woodstock Road, Oxford, UK). For the NEO study we obtained data from a measurement station from the Koninklijk Nederlands Meteorologisch Instituut (Royal Dutch Meteorological Institute).

NMR-based metabolic biomarker profiling

We used a high-throughput proton NMR metabolomics platform [14] (Nightingale Health Ltd., Helsinki, Finland) to

quantify 148 lipid and metabolite concentrations in fasting serum samples. The NMR spectroscopy was conducted at the Medical Research Council Integrative Epidemiology Unit (MRC IEU) at the University of Bristol, Bristol, United Kingdom, and processed by Nightingale's biomarker quantification algorithms (version 2014). This method provides quantification of lipoprotein subclass profiling with lipid concentrations within 14 lipoprotein subclasses. The 14 subclass sizes were defined as follows: extremely large VLDL with particle diameters from 75 nm upwards and a possible contribution of chylomicrons, five VLDL subclasses (average particle diameters of 64.0 nm, 53.6 nm, 44.5 nm, 36.8 nm, and 31.3 nm), IDL (28.6 nm), three LDL subclasses (25.5 nm, 23.0 nm, and 18.7 nm), and four HDL subclasses (14.3 nm, 12.1 nm, 10.9 nm, and 8.7 nm). Within the lipoprotein subclasses the following components were quantified: total cholesterol, total lipids, phospholipids, free cholesterol, cholesteryl esters, and triglycerides. The mean size for VLDL, LDL and HDL particles was calculated by weighting the corresponding subclass diameters with their particle concentrations. Furthermore, 47 metabolic measures were determined that belong to classes of apolipoproteins, cholesterol, fatty acids, glycerides, phospholipids, amino acids, fluid balance, glycolysis-related metabolites, inflammation, and ketone bodies. Detailed experimentation and applications of the NMR metabolomics platform have been described previously [14], as well as representative coefficients of variations (CVs) for the metabolic biomarkers [15].

Covariates

Height and weight were measured by research nurses at the OBB and NEO study centres. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Season was derived from the date of the blood sampling (winter: December–February, spring: March–May, summer: June–August, autumn: September–November). In both cohorts, use of lipid-lowering medication was determined by medication inventory.

Statistical analysis

In the NEO study, participants with a BMI of 27 kg/m² or higher are oversampled. To correctly represent associations for the general population [16], we corrected for oversampling of participants with a BMI \geq 27 kg/m², which was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality [17], whose BMI distribution was similar to the BMI distribution of the general Dutch population. Consequently, all results were based on weighted analyses and results apply to a population-based study without oversampling of individuals with a BMI \geq 27 kg/m².

All analyses were performed using STATA version 12.1 (StataCorp LP, TX, US). Baseline characteristics of the OBB and NEO study populations were conducted separately. Continuous variables were expressed as (weighted) mean (with standard deviation [SD] for normally distributed variables or (weighted) median (inter quartile range

[IQR])) for skewed variables. Dichotomous or categorical variables were expressed as (weighted) proportion (%).

As most of the metabolic outcome variables were not normally distributed and to be able to better compare the effect sizes of the different study outcomes, we log-transformed all these variables prior to standardization to a standard normal distribution (mean = 0, s.d. = 1). Associations of mean bright sunlight and temperature with lipid and metabolite concentrations were examined using multivariable linear regression analyses for the combined population of the OBB and NEO study populations. Estimates retrieved from the analyses were subsequently meta-analysed using fixed-effects meta-analysis as implemented in the *rmeta* statistical package in R. For presentation purposes, we analysed the data per 5 °C increase in outdoor temperature and per hour increase in bright sunlight exposure. Consequently, results can be interpreted as the difference in standard deviation per unit increase in either outdoor temperature (5 °C) and bright sunlight exposure (1 h).

To study the impact of adjustment of several of the covariates in the multivariable linear regression analyses, we considered 3 different statistical models. Model 1 was adjusted for age, sex and BMI (given our earlier observation that the weather exposures were associated with BMI) [5]. Model 2 was additionally adjusted for season. Model 3 was additionally adjusted either for the mean temperature or mean hours of bright sunlight to fully dissect the two weather exposures in the present study, which were moderately correlated with each other [5]. In a sensitivity analysis, we additionally excluded individuals who used cholesterol-lowering treatment. To test the consistency of the results between the OBB and the NEO cohorts, a plot was constructed with beta estimates of the identified metabolites in both cohorts visualized against each other for outdoor temperature and bright sunlight, using the R-package *ggplot2* [18].

Given the high number of statistical tests performed in the present study, we corrected for multiple testing. The metabolic biomarkers used for the present study are correlated with each other, and therefore, conventional correction for multiple testing (e.g., Bonferroni) is too stringent. To obtain the number of independent metabolic biomarkers, we used the method as described by Li et al. [19], which takes the correlations between the different metabolic biomarkers into account. Based on this method, we found 37 independent metabolic markers. For this reason, associations were considered to be statistically significant in case the *p*-value was below 0.00134 (i.e. 0.05/37).

Results

Study population characteristics

The total study population (N = 12,284) comprised of 6368 individuals from the OBB and 5916 individuals from the NEO study (see Table 1). Compared to participants from the NEO cohort, OBB volunteers were younger (mean age 47.0 vs. 55.6 years) and had a lower mean BMI (25.9 vs 26.1 kg/m²). Mean outdoor temperature during the week

prior to blood sampling was similar between the two cohorts (10.7 °C in both cohorts) although mean hours of bright sunlight were higher in Leiden than in Oxfordshire (5.0 vs 3.8 h).

Outdoor temperature and serum metabolites

Associations between outdoor temperature and circulating levels of 148 metabolites following adjustment for age, sex, BMI, season and hours of bright sunlight in the combined study population are presented in Fig. 1. In total we identified 27 metabolites whose concentration was associated with outdoor temperature after correction for multiple testing ($p < 1.34e^{-3}$). More specifically, a higher mean outdoor temperature in the week preceding blood sampling was associated with an increased concentration of total cholesterol (β (SE) = 0.064 (0.018) SD per 5 °C, $p = 5.03e^{-4}$). Lipoprotein subfraction analysis revealed that higher outdoor temperature was most strongly associated with raised serum very small VLDL cholesterol (XS-VLDL; 0.061 (0.019) per 5 °C; $p = 1.00e^{-3}$) and IDL cholesterol (0.060 (0.019) SD per 5 °C, $p = 1.12e^{-3}$) particles and their subcomponents. A higher mean atmospheric temperature was also positively associated with increased medium HDL cholesterol (M-HDL) particle concentration (0.063 (0.018) SD per 5 °C, $p = 3.34e^{-3}$) although, no associations between environmental temperature and serum LDL cholesterol (sub) particles were detected.

In addition to increased serum lipid particles, a higher mean outdoor temperature was also associated with lower circulating concentrations of unsaturated fatty acids (-0.1212 (0.0186) SD per 5 °C, $p = 7.20e^{-11}$). Finally, positive associations were detected between mean outdoor temperature and serum concentrations of the amino acids leucine (0.066 (0.016) SD per 5 °C, $p = 6.44e^{-05}$), phenylalanine (0.111 (0.018) SD per 5 °C, $p = 1.25e^{-09}$) and tyrosine (0.066 (0.018) SD per 5 °C, $p = 2.23e^{-4}$) as well as

the anaerobic glycolysis end-product lactate (0.070 (0.018) SD per 5 °C, $p = 7.64e^{-5}$). Directionally similar associations were detected in the OBB and NEO cohorts (Fig. 2, Supplementary Tables 1 and 2), although effect sizes were generally larger in the OBB. Results did not materially change after excluding individuals using cholesterol-lowering medications (data not shown).

Bright sunlight and serum metabolites

Associations between outdoor bright sunlight and NMR spectroscopy measured serum metabolites following adjustment for age, sex, BMI, season and outdoor temperature in the combined OBB and NEO population are presented in Fig. 3. After accounting for multiple testing ($p < 1.34e^{-3}$) mean outdoor bright sunlight was significantly associated with circulating levels of 58 metabolites. Contrasting the pattern of associations detected with higher temperature, a longer duration of bright sunlight during the week preceding the study visit was associated with decreased serum levels of total cholesterol (-0.019 (0.005) SD per 1 h bright sunlight, $p = 2.36e^{-4}$), VLDL cholesterol (-0.024 (0.005) SD per 1 h bright sunlight, $p = 8.06e^{-6}$) and remnant cholesterol (-0.021 (0.005) SD per 1 h bright sunlight, $p = 8.43e^{-6}$). More specifically, we found lower serum concentrations of extremely large VLDL cholesterol (XXL-VLDL: -0.020 (0.005) SD per 1 h bright sunlight, $p = 3.28e^{-5}$), very large VLDL cholesterol (XL-VLDL: -0.020 (0.005) SD per 1 h bright sunlight, $p = 5.76e^{-5}$), very small VLDL cholesterol (XS-VLDL: -0.022 (0.005) SD per 1 h bright sunlight, $p = 5.26e^{-5}$) and IDL cholesterol (-0.019 (0.005) SD per 1 h bright sunlight, $p = 4.53e^{-4}$) particles and their subcomponents. No association between bright sunlight hours and serum LDL cholesterol concentration was detected. The lower VLDL and IDL cholesterol particle numbers in the presence of increased bright sunlight duration was also reflected in the negative association between hours of bright sunlight and serum levels of ApoB (-0.020 (0.005) SD per 1-h bright sunlight, $p = 2.14e^{-4}$).

In addition to lower serum VLDL and IDL lipoprotein particle concentrations, longer bright sunlight duration was associated with a higher systemic concentration of unsaturated fatty acids (0.018 (0.005) SD per 1-h bright sunlight, $p = 8.19e^{-4}$). Finally, negative associations between ambient bright sunlight hours and serum levels of the amino acid phenylalanine (-0.018 (0.005) SD per 1 h bright sunlight, $p = 9.12e^{-4}$), and the branched-chain amino acids isoleucine (-0.019 (0.005) SD per 1 h bright sunlight, $p = 2.72e^{-4}$), leucine (-0.016 (0.005) SD per 1 h bright sunlight, $p = 1.15e^{-3}$) and valine (-0.022 (0.005) SD per 1 h bright sunlight, $p = 1.15e^{-5}$) were also detected. Indeed, bright sunlight duration was generally inversely associated with circulating levels of all the amino acids examined herein although most associations became non-significant after correction for multiple testing.

As shown in Fig. 4 and in Supplementary Tables 3 and 4, with the notable exception of leucine, glucose, glycoprotein, and total phosphoglyceride levels the associations

Table 1 Characteristics of the study populations.

	OBB (N = 6368)	NEO (N = 5916)
Age in years, mean (SD)	47.0 (7.0)	55.6 (6.0)
Men, %	43.8	43.3
Body mass index in kg/m ² , mean (SD)	25.9 (4.6)	26.1 (4.3)
Winter, %	24.1	23.9
Spring, %	26.3	26.3
Summer, %	25.2	24.3
Autumn, %	24.5	25.5
Outdoor temperature (7 days) in °C, mean (IQR)	10.7 (6.8, 15.1)	10.7 (6.9, 15.5)
Outdoor bright sunlight (7 days) in hours, median (IQR)	3.8 (2.3, 5.8)	5.0 (2.7, 7.0)

Results of the NEO study population are weighted towards the body mass distribution of the general population. Abbreviations: IQR, interquartile range; NEO, Netherlands Epidemiology of Obesity; N, number of participants; SD, standard deviation.

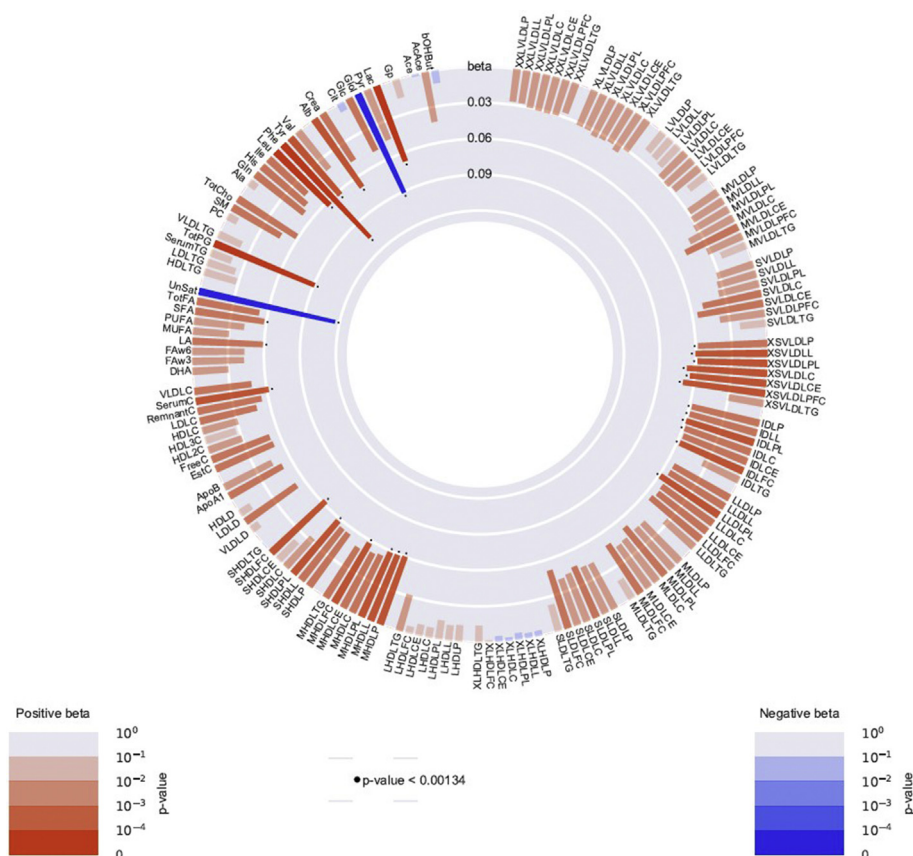


Figure 1 Observational associations between outdoor temperature and 148 lipid and metabolite biomarkers, in a meta-analysis of the Oxford Bio Bank (OBB) study (N = 6368) and Netherlands Epidemiology of Obesity (NEO) study (N = 5916). Bar heights represent the magnitude of the beta-coefficient from linear regression, which is expressed as mean SD difference in metabolic measure per 5 °C. Red bars indicate positive betas and blue bars indicate negative betas. The transparency of the bars indicates the level of statistical significance. A p -value $< 1.34 \times 10^{-3}$ is considered as statistically significant, as represented by the black dots. Results are adjusted for age, sex, BMI, season and mean hours of bright sunlight. Full names and descriptions of metabolic measures are listed in [Supplementary Table 1](#). Results of the NEO study population are weighted towards the body mass distribution of the general population. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

between bright sunlight duration and plasma metabolites were directionally identical in the OBB and NEO datasets.

Discussion

We compiled data from two population-based European cohorts, comprising a combined sample size of more than 12,000 non-diabetic individuals, to investigate the associations between mean outdoor temperature and bright sunlight duration and serum metabolites. Our results highlight that higher outdoor temperature is associated with an unfavourable metabolic profile [20–22]. In contrast, prolonged duration of bright sunlight is characterized by lower plasma lipoprotein concentrations and potentially decreased circulating levels of BCAAs. We note that the effect sizes of environmental temperature changes and bright sunlight duration on blood metabolite levels were small. However, as the data presented reflect a short exposure time to each environmental condition (fraction of one week), it is likely that the results reported here will

translate to a significant cumulative health impact over the lifetime of an individual. Furthermore, the present findings may have consequences for the population as a whole, as well as, being of interest to researchers exploring the impact of the (changing) environment on metabolism.

Our findings build on our earlier study in which we reported that bright sunlight, but not outdoor temperature, was associated with enhanced glucose and lipid metabolism [5]. Extending these findings, we now show that increased bright sunlight duration is particularly associated with lower levels of ApoB, the primary apolipoprotein of chylomicrons, VLDL, IDL, and LDL particles. We also found an association between bright sunlight duration and circulating levels of branched-chain amino acids (BCAAs). However, this result should be interpreted with caution as the effect sizes were considerably different between the OBB and NEO, and in case of the BCAA leucine, had opposite directions. Both dyslipidaemia and increased plasma levels of BCAA have been associated with an increased risk of incident T2D [20,22] and cardiovascular disease [21]. In particular, BCAAs might be causally

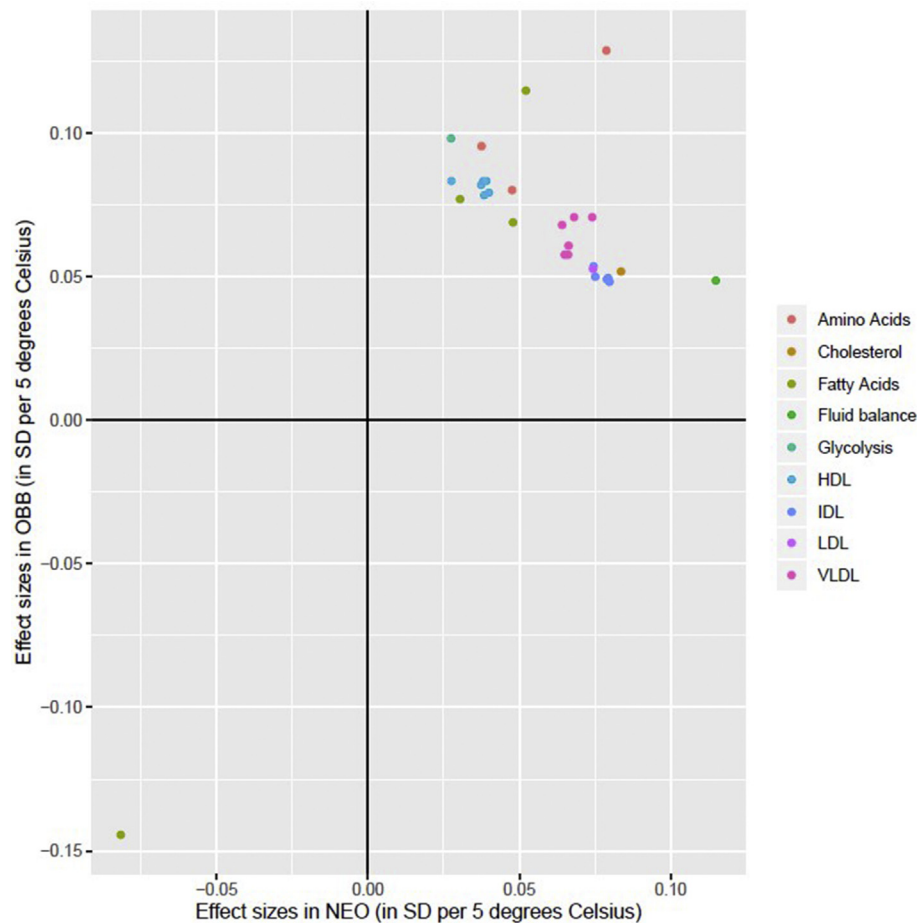


Figure 2 Correlations between the SD of the effect sizes per 5 °C of the OBB and the NEO study. Only metabolites that were significantly associated ($p < 1.34e^{-3}$) with outdoor temperature were included. X-axis presents the beta estimates per 5 °C in the Netherlands Epidemiology of Obesity (NEO) study; Y-axis presents the beta estimates per 5 °C in Oxford Biobank (OBB).

related to T2D [23] whilst increased plasma levels of VLDL cholesterol are known to be associated with poor glycaemic control [22] which contributes to the increased cardiovascular risk associated with T2D. Collectively, these results suggest that during periods of increased bright sunlight duration, individuals experience a lower risk of cardiometabolic diseases which maybe predominantly attributable to lower concentrations of VLDL (sub)particles. In contrast, the reverse might be true during spells of high environmental temperature.

We previously raised the hypothesis that the association between bright sunlight and a favourable metabolic profile is mediated, at least in part, by the influence of sunlight on melatonin metabolism [5]. Consistent with this notion, nocturnal melatonin concentrations increase with prolonged exposure to bright sunlight [24] and melatonin has been shown to play an important role in the circadian rhythm of insulin secretion by pancreatic β -cells [25]. Moreover, common and rare genetic variants at , the melatonin receptor gene are strongly associated with fasting glucose levels and T2D-risk [26,27] whilst treatment with melatonin was associated with an improved blood pressure and lipid profile both in patients with the metabolic syndrome and post-menopausal women

[28,29]. Melatonin supplementation was also shown to increase BAT volume and activity in subjects with melatonin deficiency [30]. In keeping with these findings we have recently provided genetic evidence linking sleep duration to lipid profile [31]. To further investigate this hypothesis, future studies investigating the effects of light therapy on melatonin levels and systemic metabolism are necessary [32]. Another potential mechanism underlying the observed associations between bright sunlight and a favourable cardiometabolic profile could involve vitamin D metabolism [33]. However, animal models with adipose-specific overexpression or knockout of the *VDR* via the *FABP4* promoter/enhancer element do not support a major role for vitamin D metabolism in mediating the associations between sunlight hours and the metabolome [34,35]. Furthermore, Mendelian Randomization studies have shown a lack of causal association between circulating vitamin D levels and T2D as well as lipid levels and cause-specific vascular disease and mortality [36,37]. Similarly, genetic variation in the Vitamin D Receptor gene (*VDR*) has not been linked to either T2D or coronary artery disease risk [38,39]. In animal studies ultraviolet radiation was shown to suppress weight gain and enhance glucose and lipid metabolism by stimulating nitric oxide production in

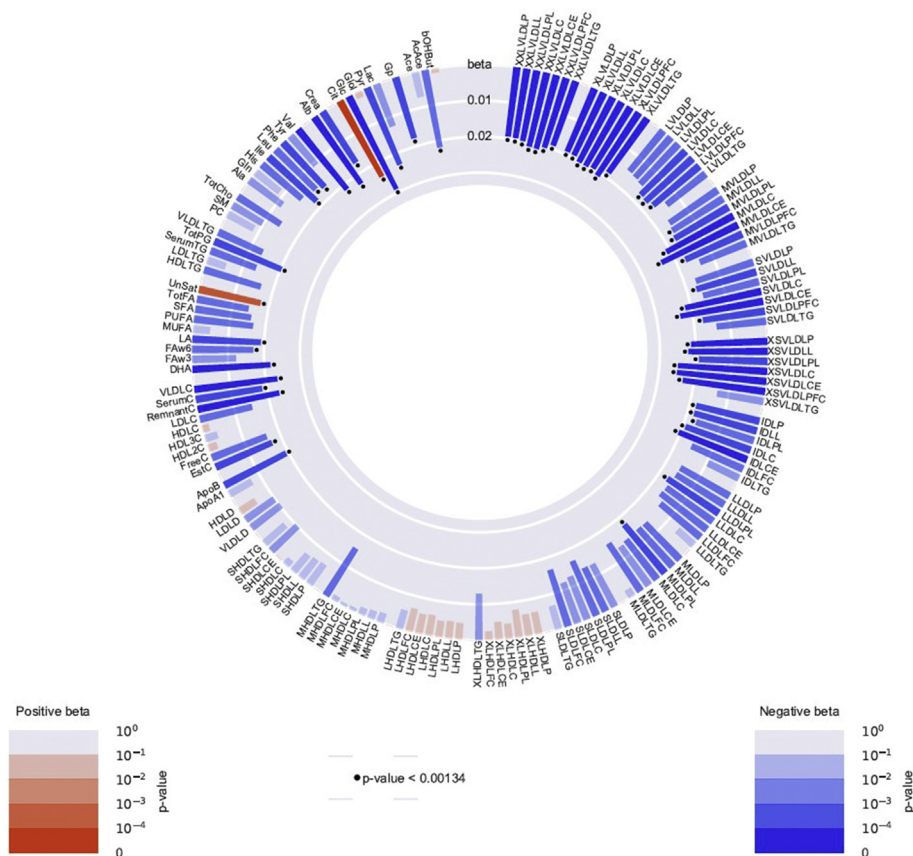


Figure 3 Observational associations between bright sunlight and 148 lipid and metabolite biomarkers, in a meta-analysis of the Oxford Bio Bank (OBB) study (N = 6368) and Netherlands Epidemiology of Obesity (NEO) study (N = 5916). Bar heights represent the magnitude of the beta-coefficient from linear regression, which is expressed as mean SD difference in metabolic measure per hour of sunlight. Red bars indicate positive betas and blue bars indicate negative betas. The transparency of the bars indicates the level of statistical significance. A p -value $< 1.34e^{-3}$ is considered as statistically significant, as represented by the black dots. Results are adjusted for age, sex, BMI, season and mean outdoor temperature. Full names and descriptions of metabolic measures are listed in [Supplementary Table 1](#). Results of the NEO study population are weighted towards the body mass distribution of the general population. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

the skin [40]. This could also provide a link between sunlight exposure and improved systemic metabolism. Finally, changes in the circulating levels of prolactin, the secretion of which was shown to be altered as a result of bright light exposure [41], may also contribute to the associations between sunlight and the plasma metabolome. In contrast, normal and modestly elevated circulating prolactin levels were inversely associated with T2D, insulin resistance, obesity, glucose intolerance, and non-alcoholic fatty liver disease [42]. In mouse models, prolactin receptor (PRLR) knockout or adenovirus-mediated PRLR knockdown in the liver in C57BL/6 mice, resulted in impaired insulin sensitivity, fatty liver, and adipocyte hypertrophy [43,44]. In contrast, on a 129SVJ background, PRLR knockout conferred resistance to high-fat-diet-induced obesity due to increased energy expenditure secondary to browning of white adipose tissue [45]. These hypotheses should be further explored in future mechanistic studies and larger epidemiological analyses.

A possible mechanism underlying the associations between increased outdoor temperature and an unfavourable metabolite profile is altered BAT function. Brown adipocytes are activated by cold and combust

intracellularly stored triglycerides to generate heat [46]. Additionally, it has been shown that activated BAT takes up glucose and lipids to supplement its intracellular triglyceride stores [47,48] and that both the presence and activity of BAT are negatively associated with outdoor temperature [49,50]. A strong association was also found between winter season and the presence and activity of BAT as measured by positron emission tomography [50,51]. Based on these data, it is possible that a higher outdoor temperature leads to an unfavourable glucose and lipid profile through impaired BAT activity. Nevertheless, testing of this hypothesis is complicated given the diluting effect of clothing and indoor heating on BAT activation during spells of cold environmental temperature in real-life. In addition to BAT activity, changes in prolactin concentrations could also partly explain the observed associations between increased outdoor temperature and a detrimental metabolite profile. Mechanistically, low temperature (e.g., daily work in a cold outdoor environment [52]) was shown to be associated with lower circulating prolactin, although no seasonal effect on plasma prolactin levels has been described [53]. Finally, it should be noted that our observations could also be attributable, wholly or at least in part

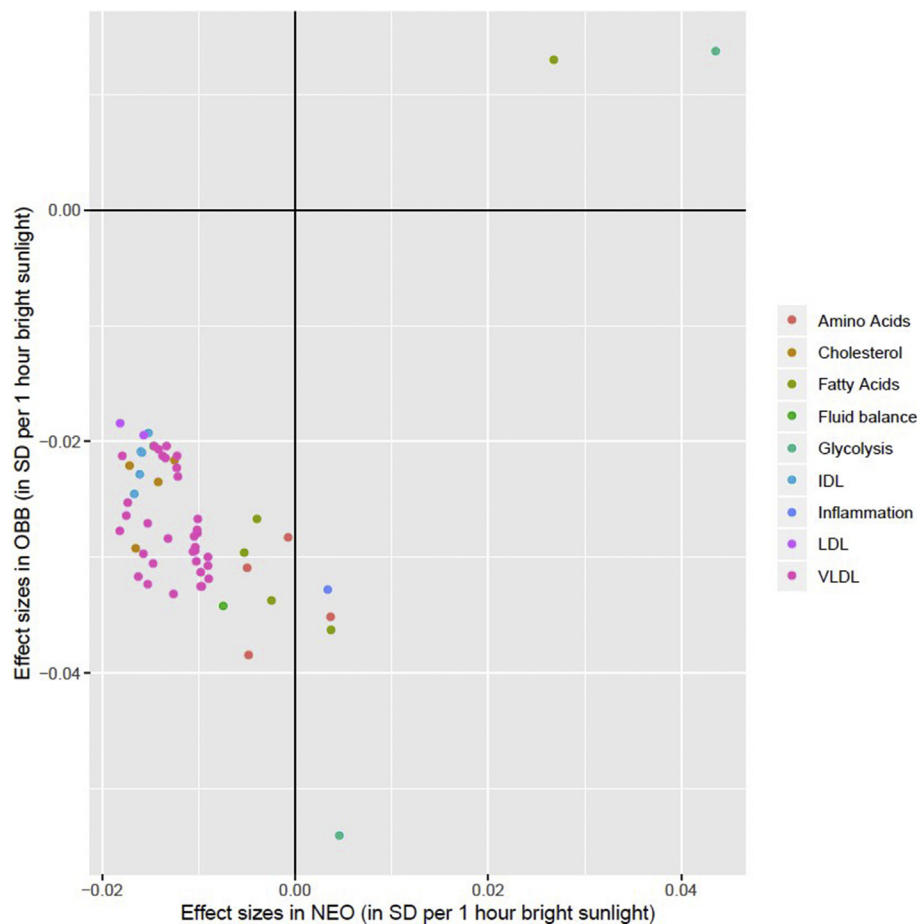


Figure 4 Correlations between the SD of the effect sizes per hour of bright sunlight of the OBB and the NEO study. Only metabolites that were significantly associated ($p < 1.34e^{-3}$) with bright sunlight were included. X-axis presents the beta estimates per hour bright sunlight in the Netherlands Epidemiology of Obesity (NEO) study; Y-axis presents the beta estimates per hour bright sunlight in Oxford Biobank (OBB).

to lifestyle changes dependent on outdoor temperature and/or bright sunlight duration. For example, the population-based Rotterdam Study showed a clear seasonal pattern in diet with higher dietary quality in winter [54]. Unfortunately, due to the lack of actual physical activity and dietary intake data in the OBB coupled with small effect sizes in NEO, we were not able to test the impact of lifestyle changes in response to variations in weather conditions on the metabolome. Nevertheless, additional adjustment for season, which would partially adjust for variations in lifestyle factors, did not materially alter our findings.

A major strength of our study is that we were able to combine data from two large independent cohorts originating from two different countries and comprising more than 12,000 participants in order to study the effects of temperature and bright sunlight on metabolism. In addition, we made use of detailed independently collected data from local weather stations. A limitation is the inherent heterogeneity in the two cohorts, which must be considered when interpreting the results. Potential confounding effects might have been driven by differences in lifestyle between the United Kingdom and The Netherlands. Although not a source of bias, another limitation is that we can only assume that the study participants were actually

exposed to higher outdoor temperatures and bright sunlight during the research period. This might have resulted in some random misclassification, and an underestimation of the effect estimates.

In summary, extending our earlier work [5], we provide further evidence that increased bright sunlight may be associated with improved cardiometabolic health. In contrast increased outdoor temperature may be associated with an adverse cardiometabolic profile. Future research is required to elucidate the mechanistic basis of the observed associations.

Data availability

Data is available on request after approval of a study protocol by the boards of the Oxford Biobank and Netherlands Epidemiology of Obesity Study.

Funding

The Oxford Biobank is supported by the NIHR Oxford BRC Obesity and Lifestyle theme. The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area

'Vascular and Regenerative Medicine'. FK is supported by British Heart Foundation (RG/17/1/32663). CC is a BHF Intermediate clinical research fellow. SK is supported by the Dutch Heart Foundation, the Netherlands (2017T016). We acknowledge the support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation (CVON2014-02 ENERGISE).

Author contribution

Boukje C. Eveleens Maarse: Formal Analysis, Writing – Original Draft. Nelli Y. Loh: Data Curation, Investigation, Writing – Review and Editing. Fredrik Karpe: Resources, Data Curation, Writing – Review and Editing. Frits R. Rosendaal: Resources, Data Curation, Writing – Review and Editing. Diana van Heemst: Resources, Data Curation, Writing – Review and Editing. Dennis O. Mook-Kanamori: Resources, Data Curation, Writing – Review and Editing. Ko Willems van Dijk: Resources, Data Curation, Writing – Review and Editing. Patrick C.N. Rensen: Resources, Data Curation, Writing – Review and Editing; Sander Kooijman: Conceptualization, Formal Analysis, Writing – Original Draft, Supervision, Project Administration. Constantinos Christodoulides: Conceptualization, Formal Analysis, Writing – Review and Editing, Supervision, Project Administration. Raymond Noordam: Conceptualization, Formal Analysis, Software, Writing – Original Draft, Visualization, Supervision, Project Administration.

Declaration of competing interest

Dr. Dennis Mook-Kanamori is a part-time research consultant at Metabolon, Inc. All other authors declare to have no conflict of interest.

Acknowledgements

We express our gratitude to all individuals who participate in the OBB and NEO study. We are grateful to all participating general practitioners for inviting eligible participants and all research nurses for collecting the data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.numecd.2020.07.030>.

References

- van den Berg R, Kooijman S, Noordam R, Ramkisoensing A, Abreu-Vieira G, Tambyrajah LL, et al. A diurnal rhythm in brown adipose tissue causes rapid clearance and combustion of plasma lipids at waking. *Cell Rep* 2018;22:3521–33.
- Speakman JR, Heidari-Bakavoli S. Type 2 diabetes, but not obesity, prevalence is positively associated with ambient temperature. *Sci Rep* 2016;6:30409.
- Valdés S, Gamgaram VKD, Lago A, García-Torres F, Badía-Guillén R, Oliveira G, et al. Ambient temperature and prevalence of diabetes and insulin resistance in the Spanish population: Di@bet.es study 2019;1.
- Blauw LL, Aziz NA, Tannemaat MR, Blauw CA, de Craen AJ, Pijl H, et al. Diabetes incidence and glucose intolerance prevalence increase with higher outdoor temperature. *BMJ Open Diabetes Res Care* 2017;5:e000317.
- Noordam R, Ramkisoensing A, Loh NY, Neville MJ, Rosendaal FR, Willems van Dijk K, et al. Associations of outdoor temperature, bright sunlight, and cardiometabolic traits in two European population-based cohorts. *J Clin Endocrinol Metab* 2019;104:2903–10.
- Nicholson JK, Holmes E, Kinross JM, Darzi AW, Takats Z, Lindon JC. Metabolic phenotyping in clinical and surgical environments. *Nature* 2012;491:384–92.
- Fischer K, Kettunen J, Wurtz P, Haller T, Havulinna AS, Kangas AJ, et al. Biomarker profiling by nuclear magnetic resonance spectroscopy for the prediction of all-cause mortality: an observational study of 17,345 persons. *PLoS Med* 2014;11:e1001606.
- Wurtz P, Havulinna AS, Soininen P, Tynkkynen T, Prieto-Merino D, Tillin T, et al. Metabolite profiling and cardiovascular event risk: a prospective study of 3 population-based cohorts. *Circulation* 2015;131:774–85.
- Tynkkynen J, Chouraki V, van der Lee SJ, HERNESNIEMI J, Yang Q, Li S, et al. Association of branched-chain amino acids and other circulating metabolites with risk of incident dementia and Alzheimer's disease: a prospective study in eight cohorts. *Alzheimers Dement* 2018;14:723–33.
- Wang TJ, Larson MG, Vasani RS, Cheng S, Rhee EP, McCabe E, et al. Metabolite profiles and the risk of developing diabetes. *Nat Med* 2011;17:448–53.
- Shah SH, Kraus WE, Newgard CB. Metabolomic profiling for the identification of novel biomarkers and mechanisms related to common cardiovascular diseases: form and function. *Circulation* 2012;126:1110–20.
- Karpe F, Vasani SK, Humphreys SM, Miller J, Cheeseman J, Louise Dennis A, et al. Cohort profile: the Oxford Biobank. *Int J Epidemiol* 2017.
- de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. *Eur J Epidemiol* 2013;28:513–23.
- Soininen P, Kangas AJ, Würtz P, Suna T, Ala-Korpela M. Quantitative serum nuclear magnetic resonance metabolomics in cardiovascular epidemiology and genetics. *Circ Cardiovasc Genet* 2015;8:192–206.
- Kettunen J, Demirkan A, Wurtz P, Draisma HH, Haller T, Rawal R, et al. Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of LPA. *Nat Commun* 2016;7:11122.
- Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. *Am J Public Health* 1991;81:1166–73.
- Lumley T. Analysis of complex survey samples. 2004. <http://www.jstatsoft.org/v09/i08/paper>. [Accessed 5 August 2020].
- Wickham H. ggplot2: Elegant graphics for data analysis. New York: Springer-Verlag; 2016.
- Li J, Ji L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Heredity* 2005;95:221–7.
- Ahola-Olli AV, Mustelin L, Kalimeri M, Kettunen J, Jokelainen J, Auvinen J, et al. Circulating metabolites and the risk of type 2 diabetes: a prospective study of 11,896 young adults from four Finnish cohorts. *Diabetologia* 2019;62(12):2298–309.
- Holmes MV, Millwood IY, Kartsonaki C, Hill MR, Bennett DA, Boxall R, et al. Lipids, lipoproteins, and metabolites and risk of myocardial infarction and stroke. *J Am Coll Cardiol* 2018;71:620–32.
- Wang J, Stancakova A, Soininen P, Kangas AJ, Paananen J, Kuusisto J, et al. Lipoprotein subclass profiles in individuals with varying degrees of glucose tolerance: a population-based study of 9399 Finnish men. *J Intern Med* 2012;272:562–72.
- Lotta LA, Scott RA, Sharp SJ, Burgess S, Luan J, Tillin T, et al. Genetic predisposition to an impaired metabolism of the branched-chain amino acids and risk of type 2 diabetes: a Mendelian randomisation analysis. *PLoS Med* 2016;13:e1002179.
- Park SJ, Tokura H. Bright light exposure during the daytime affects circadian rhythms of urinary melatonin and salivary immunoglobulin A. *Chronobiol Int* 1999;16:359–71.
- Peschke E, Bahr I, Muhlbauer E. Melatonin and pancreatic islets: interrelationships between melatonin, insulin and glucagon. *Int J Mol Sci* 2013;14:6981–7015.

- [26] Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, Sparso T, Holmkvist J, Marchand M, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet* 2009;41:89–94.
- [27] Bonnefond A, Clement N, Fawcett K, Yengo L, Vaillant E, Guillaume JL, et al. Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes. *Nat Genet* 2012;44:297–301.
- [28] Kozirog M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. *J Pineal Res* 2011;50:261–6.
- [29] Tamura H, Nakamura Y, Narimatsu A, Yamagata Y, Takasaki A, Reiter RJ, et al. Melatonin treatment in peri- and postmenopausal women elevates serum high-density lipoprotein cholesterol levels without influencing total cholesterol levels. *J Pineal Res* 2008;45:101–5.
- [30] Halpern B, Mancini MC, Bueno C, Barcelos IP, de Melo ME, Lima MS, et al. Melatonin increases brown adipose tissue volume and activity in patients with melatonin deficiency: a proof-of-concept study. *Diabetes* 2019;68:947–52.
- [31] Bentley AR, Sung YJ, Brown MR, Winkler TW, Kraja AT, Ntalla I, et al. Multi-ancestry genome-wide gene-smoking interaction study of 387,272 individuals identifies new loci associated with serum lipids. *Nat Genet* 2019;51:636–48.
- [32] Brouwer A, van Raalte DH, Diamant M, Rutters F, van Someren EJ, Snoek FJ, et al. Light therapy for better mood and insulin sensitivity in patients with major depression and type 2 diabetes: a randomised, double-blind, parallel-arm trial. *BMC Psychiatr* 2015;15:169.
- [33] Pilz S, Kienreich K, Rutters F, de Jongh R, van Ballegooijen AJ, Grubler M, et al. Role of vitamin D in the development of insulin resistance and type 2 diabetes. *Curr Diabetes Rep* 2013;13:261–70.
- [34] Mutt SJ, Hypponen E, Saarnio J, Jarvelin MR, Herzig KH. Vitamin D and adipose tissue—more than storage. *Front Physiol* 2014;5:228.
- [35] Matthews DG, D'Angelo J, Drellich J, Welsh J. Adipose-specific Vdr deletion alters body fat and enhances mammary epithelial density. *J Steroid Biochem Mol Biol* 2016;164:299–308.
- [36] Ye Z, Sharp SJ, Burgess S, Scott RA, Imamura F, Langenberg C, et al. Association between circulating 25-hydroxyvitamin D and incident type 2 diabetes: a mendelian randomisation study. *Lancet Diabetes Endocrinol* 2015;3:35–42.
- [37] Huang T, Afzal S, Yu C, Guo Y, Bian Z, Yang L, et al. Vitamin D and cause-specific vascular disease and mortality: a Mendelian randomisation study involving 99,012 Chinese and 106,911 European adults. *BMC Med* 2019;17:160.
- [38] Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015;47:1121–30.
- [39] Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 2018;50:1505–13.
- [40] Geldenhuys S, Hart PH, Endersby R, Jacoby P, Feelisch M, Weller RB, et al. Ultraviolet radiation suppresses obesity and symptoms of metabolic syndrome independently of vitamin D in mice fed a high-fat diet. *Diabetes* 2014;63:3759–69.
- [41] Kostoglou-Athanassiou I, Treacher DF, Wheeler MJ, Forsling ML. Bright light exposure and pituitary hormone secretion. *Clin Endocrinol (Oxf)*. 1998;48:73–9.
- [42] Macotela Y, Triebel J, Clapp C. Time for a new perspective on prolactin in metabolism. *Trends Endocrinol Metab* 2020;31:276–86.
- [43] Ruiz-Herrera X, de Los Rios EA, Diaz JM, Lerma-Alvarado RM, Martinez de la Escalera L, Lopez-Barrera F, et al. Prolactin promotes adipose tissue fitness and insulin sensitivity in obese males. *Endocrinology* 2017;158:56–68.
- [44] Yu J, Xiao F, Zhang Q, Liu B, Guo Y, Lv Z, et al. PRLR regulates hepatic insulin sensitivity in mice via STAT5. *Diabetes* 2013;62:3103–13.
- [45] Freemark M, Fleenor D, Driscoll P, Binart N, Kelly P. Body weight and fat deposition in prolactin receptor-deficient mice. *Endocrinology* 2001;142:532–7.
- [46] Hoeke G, Kooijman S, Boon MR, Rensen PC, Berbee JF. Role of brown fat in lipoprotein metabolism and atherosclerosis. *Circ Res* 2016;118:173–82.
- [47] Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med* 2009;360:1518–25.
- [48] Schilperoord M, Hoeke G, Kooijman S, Rensen PC. Relevance of lipid metabolism for brown fat visualization and quantification. *Curr Opin Lipidol* 2016;27:242–8.
- [49] Ouellet V, Routhier-Labadie A, Bellemare W, Lakkhal-Chaieb L, Turcotte E, Carpentier AC, et al. Outdoor temperature, age, sex, body mass index, and diabetic status determine the prevalence, mass, and glucose-uptake activity of 18F-FDG-detected BAT in humans. *J Clin Endocrinol Metab* 2011;96:192–9.
- [50] Yoneshiro T, Matsushita M, Nakae S, Kameya T, Sugie H, Tanaka S, et al. Brown adipose tissue is involved in the seasonal variation of cold-induced thermogenesis in humans. *Am J Physiol Regul Integr Comp Physiol* 2016;310:R999–r1009.
- [51] Au-Yong IT, Thorn N, Ganatra R, Perkins AC, Symonds ME. Brown adipose tissue and seasonal variation in humans. *Diabetes* 2009;58:2583–7.
- [52] Solter M, Misjak M. Pituitary-gonadal response to extreme cold exposure in healthy men. *Horm Metab Res* 1989;21:343–4.
- [53] Gala RR, Van De Walle C, Hoffman WH, Lawson DM, Pieper DR, Smith SW, et al. Lack of a circannual cycle of daytime serum prolactin in man and monkey. *Acta Endocrinol (Copenh)*. 1977;86:257–62.
- [54] van der Toorn JE, Cepeda M, Kiefte-de Jong JC, Franco OH, Voortman T, Schoufour JD. Seasonal variation of diet quality in a large middle-aged and elderly Dutch population-based cohort. *Eur J Nutr* 2020;59:493–504.