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Lifestyle may modify the glucose-raising effect of genetic loci. A study in the Greek population

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Abstract *Background and aims:* Lifestyle habits including dietary intake and physical activity are closely associated with multiple body processes including glucose metabolism and are known to affect human health. Recent genome-wide association studies have identified several single nucleotide polymorphisms (SNPs) associated with glucose levels. The hypothesis tested here is whether a healthy lifestyle assessed via a score is associated with glycaemic traits and whether there is an interaction between the lifestyle and known glucose-raising genetic variants in association with glycaemic traits.
Methods and results: Participants of Greek descent from the THISEAS study were included in this analysis. We developed a glucose preventive score (GPS) including dietary and physical activity characteristics. We also modelled a weighted genetic risk score (wGRS), based on 20 known glucose-raising loci, in order to investigate the impact of lifestyle–gene interaction on glucose levels. The GPS was observed to be significantly associated with lower glucose concentrations ($\beta \pm$ SE: -0.083 ± 0.021 mmol/L, $P = 1.6 \times 10^{-04}$) and the wGRS, as expected, with increased glucose levels ($\beta \pm$ SE: 0.020 ± 0.007 mmol/L, $P = 8.4 \times 10^{-3}$). The association of the wGRS with glucose levels was attenuated after interaction with the GPS. A higher GPS indicated decreasing glucose levels in the presence of an increasing wGRS ($\beta_{interaction} \pm$ SE: -0.019 ± 0.007 mmol/L, $P = 0.014$).
Conclusion: Our results indicate that lower glucose levels underlie a healthier lifestyle and also support an interaction between the wGRS for known glycaemic loci and GPS associated with lower glucose levels. These scores could be useful tools for monitoring glucose metabolism.
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Introduction

Glucose homeostasis deficiency may lead to chronic increase in blood glucose levels and could affect a large number of tissues and organs. The shift from early metabolic abnormalities that forego diabetes, such as impaired fasting glucose and impaired glucose tolerance, to diabetes is not direct. However, current evidence indicates that most individuals with pre-diabetic states finally develop diabetes [1–3]. Cardiovascular disease risk moderately increases during the pre-diabetic state [4], but it further increases with the development of diabetes, along with long-term complications affecting

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eyes, kidneys and nervous system. As the medical socioeconomic strain of type 2 diabetes mellitus is increased by its complications and highlights the burden on healthcare systems [5]. The number of single nucleotide polymorphisms (SNPs) associated with fasting glucose concentration levels has now increased to 36 [6]. A combination of genetic and environmental factors contributes to impaired glucose homeostasis [7]. A large number of genome-wide significant genetic loci associated with glycaemic traits [6] and type 2 diabetes development [8] have been recently identified. In addition to genetic factors involved in impaired glucose homeostasis, lifestyle patterns including dietary intake play a significant role in the pathogenic process [7,9–11]. Glycaemic control strategies include weight management as the primary nutritional strategy, accompanied by moderate physical activity [12,13]. Evaluation of a dietary pattern (rather than single nutrients) and exercise status have been used in nutritional epidemiology and could provide a direct approach to the quantification of disease prevention [14,15]. The optimal prevention of diabetes requires identification of its modifiable risk factors to be targeted for intervention. Investigation of the interactions between genetic variants and environment has helped elucidate the biological basis of diabetes mellitus and promote individualised health-promoting lifestyle recommendations [16]. Information on personal genetic profile and lifestyle components are touted for potential contribution to personalised medicine [17]. It is of great interest for clinicians and other health-related professionals to consider the impact of diet and physical activity on modification of glucose levels in individuals with increased genetic predisposition.

In the present study, we sought to 1) evaluate the association of a healthy lifestyle pattern in the Greek population, by means of a preventive score, with glycaemic and adiposity traits and 2) evaluate whether this lifestyle pattern modifies the association of known glucose-raising genetic variants on glycaemic traits.

Methods

Study population

Our sample consisted of unrelated individuals of Greek origin, aged 57.7 ± 14.1 years, drawn from the THISEAS (The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility) [18]. Individuals with type 2 diabetes (medical history or fasting glucose levels >7 mmol/L) and outliers with respect to energy intake were excluded (Supplementary Methods). Information about genotyping, the description of adiposity and biochemical measurements, as well as the assessment of dietary patterns and physical activity are provided in the Supplementary Material (Supplementary Methods).

Modelling of glucose preventive score (GPS) and weighted genetic risk score (wGRS)

Based on selected dietary and physical activity data, a 'Glucose Preventive Score' for each volunteer was calculated. The components used for the score showed a positive or negative association with glucose levels and are supported in literature (Supplementary Methods). The lifestyle parameters used for the score included three with glucose-lowering association (hours in movement during work per day, vegetable consumption (servings per day) and fruits and fresh juice; servings/day) and one with glucose-raising association (consumption of soft drinks and beverages with sugar; servings per day). Daily servings of the food groups were estimated in our sample as the sum of daily servings of each item included on the food frequency questionnaire [19]. The lifestyle variables were categorised in tertiles and each tertile received a point. The first three components were assigned increasing points per tertile and the last one decreasing points. The score was the sum of points for all components per individual. The score ranged from 0- to 10 points, with an increasing glucose-lowering effect (Supplemental Table 1).

In order to evaluate the cumulative association of known glucose-raising genetic variants with glucose metabolism, we constructed a weighted genetic risk score (wGRS) and an unweighted genetic risk score (GRS). We included the published sentinel SNPs from 20 glycaemic-related loci, which were identified from the MAGIC (the Meta-Analyses of Glucose and Insulin-related traits Consortium) MetaboChip Meta-analysis effort [6]. For each of the 20 SNPs, individuals carrying 0, 1 or 2 glucose-raising alleles received 0, 1 or 2 points, respectively, for the GRS estimation. The wGRS was calculated as the sum of points across the 20 SNPs weighted by their published effect sizes [6].

We then divided the score by the average effect size of all SNPs so that it is rescaled to represent the range of the possible number of weighted glucose-increasing alleles for each individual [20].

The wGRS score was split into quantiles. Individuals in the last quantile (wGRS > 25 points) were classified as high risk (12.7% of the total sample) (Supplementary Methods).

Statistical methods and analysis

Statistical methods used for the analyses are described in detail in the Supplementary Methods. Association analysis was performed using PLINK [21] and R version 3.1.1. Continuous variables are presented as mean ± standard deviation (SD) or median ± interquartile range and categorical as relative frequencies. Natural log-transformed values of insulin levels were used. The reported *p*-values were based on two-sided tests. Linear regression models assuming an additive genetic model were used to test the association of the 20 SNPs on glucose levels. Linear regression models were applied to test for the associations between each lifestyle variable and glucose levels as well

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