Associations of Common Genetic Variants With Age-Related Changes in Fasting and Postload Glucose
Evidence From 18 Years of Follow-Up of the Whitehall II Cohort

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OBJECTIVE—In the general, nondiabetic population, fasting glucose increases only slightly over time, whereas 2-h postload glucose shows a much steeper age-related rise. The reasons underlying these different age trajectories are unknown. We investigated whether common genetic variants associated with fasting and 2-h glucose contribute to age-related changes of these traits.

RESEARCH DESIGN AND METHODS—We studied 5,196 nondiabetic participants of the Whitehall II cohort (aged 40–78 years) attending up to four 5-yearly oral glucose tolerance tests. A genetic score was calculated separately for fasting and 2-h glucose, including 16 and 5 single nucleotide polymorphisms, respectively. Longitudinal modeling with age centered at 55 years was used to study the effects of each genotype and genetic score on fasting and 2-h glucose and their interactions with age, adjusting for sex and time-varying BMI.

RESULTS—The fasting glucose genetic score was significantly associated with fasting glucose with a 0.029 mmol/L (95% CI 0.023–0.034) difference ($P = 2.76 \times 10^{-21}$) per genetic score point, an association that remained constant over time (age interaction $P = 0.17$). Two-hour glucose levels differed by 0.076 mmol/L (0.047–0.105) per genetic score point ($P = 3.1 \times 10^{-7}$); notably, this effect became stronger with increasing age by 0.006 mmol/L (0.003–0.009) per genetic score point per year (age interaction $P = 3.0 \times 10^{-5}$), resulting in diverging age trajectories by genetic score.

CONCLUSIONS—Common genetic variants contribute to the age-related rise of 2-h glucose levels, whereas associations of variants for fasting glucose are constant over time, in line with stable age trajectories of fasting glucose. *Diabetes* **60:1617–1623, 2011**

Earlier longitudinal analyses of participants of the Whitehall II cohort have demonstrated a gradual and a subsequent steep increase in both fasting and postload glucose preceding the diagnosis of type 2 diabetes (1). This lends some support to a multistage model of diabetes etiology in which a compensatory and adaptive phase is followed by a period of β-cell decompensation that leads to a rapid rise in glucose levels and ultimately overt diabetes (2). In contrast, in the general, nondiabetic population, fasting glucose levels increase only slightly over time (3), whereas 2-h postload glucose shows a much steeper age-related rise (1), an effect that appears to be less pronounced at younger ages (4). The reasons underlying these different age trajectories of fasting and postload glucose in nondiabetic individuals are not well understood.

Because of the recent progress in genetic mapping, our understanding of the genetic basis of glycemic control in nondiabetic individuals has rapidly increased. Genome-wide associated studies (GWASs) using cross-sectional phenotypic data have now identified 16 loci associated with fasting and 5 loci associated with postchallenge glucose levels (5–11). Some of these loci were known or have been shown subsequently to also be associated with the risk of type 2 diabetes in independent case-control studies. Common genetic variants associated with fasting and 2-h glucose may contribute to age-related changes of these traits; however, this has not been investigated because genetic studies generally rely on a single glucose measurement or oral glucose tolerance test (OGTT) and thus are unable to investigate associations of genetic loci with changes in fasting and postload glucose levels over time or with increasing age.

We therefore set out to investigate longitudinally the influence of recently identified common genetic loci related to glucose metabolism in nondiabetic individuals, as well as derived genetic risk scores (10,11), on age-related changes of fasting and 2-h glucose over a maximum of 18 years of follow-up in the prospective Whitehall II study, using data from 5,196 participants aged 40–78 years who attended up to four 5-yearly clinic visits (13,141 glucose measurements or OGTTs).

RESEARCH DESIGN AND METHODS

All nonindustrial civil servants aged 35–55 years working in the London offices of 20 departments were invited to participate in the longitudinal Whitehall II

study. A total of 10,308 (6,895 men) subjects were recruited between 1985 and 1988 (phase 1) and followed at eight subsequent phases ~2.5 years apart (12). Every phase included a questionnaire, and every second phase additionally included a clinical examination (phases 1, 3, 5, 7, and 9). Participation in subsequent clinical phases, defined as either a returned questionnaire or clinic attendance, was 6,057 men and 2,758 women at phase 3 (1991–1993); 5,473 men and 2,397 women at phase 5 (1997–1999); 4,893 men and 2,074 women at phase 7 (2002–2004); and 4,759 men and 2,002 women at phase 9 (2007–2009). The University College London Ethics Committee reviewed and approved the study, and written informed consent was obtained from each participant at each phase. Phase 3 is considered the baseline for the purpose of this study, because it was the first clinical examination in which OGTTs were performed.

Participants were eligible for inclusion in this study if they were of European descent, had available DNA, and did not have prevalent diabetes at phase 3 (a total of 4,038 men and 1,505 women). Of 20,215 fasting or 2-h glucose observation points in these 5,543 individuals, 5,769 observations were excluded because samples were nonfasting (fasting <8 h). An additional 1,305 observations were excluded because they were obtained after a diagnosis of diabetes (a total of 627 of 5,543 included individuals [11.3%] developed diabetes during follow-up) or did not have a contemporary BMI measurement. With these restrictions, 347 individuals no longer contributed any observations and were effectively excluded, yielding the maximum study population of 5,196 individuals who contributed a total of 13,141 observation points. The number of individuals and observation points differs slightly depending upon genotype information; exact numbers are provided in Supplementary Table ST2. Information for analyses of the fasting and 2-h glucose genetic scores was available for a total of 4,008 and 3,968 individuals with 10,151 and 9,845 observation points, respectively.

Measurements

Blood glucose and diabetes. Blood samples at all phases were handled according to standard protocols. Venous blood was taken after a requested overnight fast before participants underwent a standard 75-g 2-h OGTT. The Whitehall II study protocol allowed participants with an afternoon appointment to have a light breakfast at least 5 h prior to their appointment. For the purpose of this analysis, samples obtained <8 h after the last reported meal were excluded. Glucose samples were drawn into fluoride monovette tubes and centrifuged on site within 1 h. Blood glucose was measured using the glucose oxidase method (13) on a YSI model 23A glucose analyzer (YSI, Yellow Springs, OH; phase 3, mean coefficient of variation 2.9–3.3%) and a YSI model 2300 Stat Plus analyzer (phases 5, 7, and 9, mean coefficient of variation 1.4–3.1%), as previously described (1). At each phase, diabetes was defined by World Health Organization criteria based on fasting glucose ≥7.0 mmol/L or 2-h glucose ≥11.1 mmol/L (14). Participants reporting doctor-diagnosed diabetes or the use of diabetes medications were classified as having diabetes regardless of their OGTT results. The date of diabetes diagnosis was assigned according to the interval method as the midpoint between the first visit with a diabetes diagnosis and the last visit without diabetes.

Genotyping. DNA was extracted from whole-blood samples collected at phase 7 (n = 6,311 participants with blood samples attending phase 7 and consenting to DNA analysis for a total of 6,483 attending phase 7) using magnetic bead technology (Source Bioscience LifeSciences, Nottingham, U.K.). DNA extraction was successful for 6,156 participants. Genotyping of single nucleotide polymorphisms (SNPs) associated with fasting and 2-h postload glucose was carried out using Taqman assays in all participants of European descent who had DNA available (n = 5,666). Call rates were >96% and duplicates (9%) were 99% concordant. *P* values for all SNPs were ≥ 0.04 when testing for deviation from Hardy-Weinberg equilibrium.

We included 16 SNPs in or near *MTNR1B, ADRA2A, CRY2, ADCY5, SLC2A2, TCF7L2, SLC30A8, FADS1, C2CD4B* (previously *FAM148B*), *DGKB-TMEM195, PROX1, GCK, G6PC2, GLIS3, GCKR,* and *MADD* for fasting glucose (10) and *GIPR, TCF7L2, GCKR, VPS13C,* and *ADCY5* for 2-h glucose (11). Effect alleles were defined to be the glucose-raising alleles (Supplementary Table ST2), as previously described (10,11). SNPs in *TCF7L2, GCKR,* and *ADCY5* are associated with both fasting and 2-h glucose, with SNPs in *GCKR* known to affect fasting and 2-h glucose levels in opposite directions (reflected in the allele coding for the fasting and 2-h glucose *GCKR* SNPs rs780094 and rs1260326). For these three loci, different SNPs were identified in the respective fasting and 2-h GWASs and were genotyped in this study; however, locus-specific SNPs are all in high linkage disequilibrium ($r^2 > 0.74$).

Genetic scores. Genetic scores were calculated separately for fasting and 2-h glucose. Genetic scores were defined as the additive sum of the number of glucose-raising alleles for each participant based on SNPs reaching genomewide significance in combined discovery and replication samples in published fasting or 2-h glucose GWASs. The mean SNP score (±SD) was 17.0 ± 3.0 for fasting glucose and 4.0 ± 1.4 for 2-h glucose. Sensitivity analyses were performed using weighted genetic scores for fasting and 2-h glucose based on published β-coefficients from replication samples only (10,11), where the sum

of the weights was set to the number of SNPs and the weights were proportional to the estimate of the replication effect size for each SNP.

Other covariates. Information on date of birth and sex was available from the phase 1 questionnaire. BMI (kg/m^2) was calculated from standardized measurements of weight and height taken at each clinic visit.

Statistical analysis. Statistical analyses were undertaken using SAS version 9.1 (SAS Institute, Cary, NC) and R version 2.11.1. Statistical significance was inferred at a 5% level. Trajectories of fasting and 2-h glucose were estimated using multilevel models, taking age as the underlying time scale and accounting for the dependence of measurements within individuals. This method is not sensitive to missing observation points, and individuals without complete information for all phases were included in the analyses, assuming that missing is random, with individuals with one data point contributing to cross-sectional associations and to group-level trajectories.

We first fitted nonparametric curves of individual trajectories and trajectories by tertiles of the fasting and 2-h glucose genetic scores using locally weighted scatterplot smoother. Individual trajectories of fasting and 2-h glucose were analyzed using mixed models, fitting a random intercept and slope term for both fasting and 2-h glucose (see Supplementary Methods for more detail). The overall trajectory and the group trajectories (by SNPs) of fasting and 2-h glucose were modeled as a fixed intercept and slope term, and results from these models are presented.

The effect of each SNP was modeled as a continuous variable, where the effect of having zero, one, or two glucose-raising alleles is assumed to be additive. Similarly, SNP scores were modeled as continuous variables. Curves fitted to the trajectories are characterized by their intercept (level of fasting or 2-h glucose) and slope (increase in fasting or 2-h glucose with age), and the effects of SNPs (or genetic score) on the slope are tested as SNP (genetic score) interactions with age.

All analyses were adjusted for sex and time-varying BMI, except for those performed to generate plots of changes in fasting and 2-h glucose by percentiles of each genetic score, where BMI was assumed to be constant over time for simplicity. Two- and three-way interactions between age, sex, and BMI were investigated and excluded from the final models because they were nonsignificant. The time parameter (age) was centered arbitrarily at age ~55 years for easier interpretation of parameter estimates. We built separate models for each fasting and 2-h glucose SNP and for the fasting and 2-h glucose SNP scores. A detailed model description is included in Supplementary Appendix A.

RESULTS

Population characteristics. Characteristics of participants included in the analyses at study phase 7 (the phase of DNA collection), in comparison with those participants who attended phase 7 but were excluded from analyses for any of the reasons outlined above, are shown in Supplementary Table ST1. Those excluded were more likely to be women (38.5 vs. 26.8%), were on average aged ≥1.8 years (95% CI 1.5–2.1), had a 0.6 kg/m^2 (0.4–0.9) higher BMI, and had 0.7 mmol/L (0.6–0.8) higher fasting and 0.6 mmol/L (0.4–0.7) higher 2-h glucose levels compared with participants who were eligible and included in this study. All 5,196 participants were born between 1930 and 1952, their ages ranging from 40 to 78 years during a maximum follow-up of 18 years. Details of genetic variants included in this study are shown in Supplementary Table ST2.

Population trajectories of fasting and 2-h glucose. Estimated fasting and 2-h glucose levels across the followup were 5.33 mmol/L (95% CI 5.32–5.35) and 5.84 mmol/L (5.79–5.89), respectively, for a man aged 55 years with a BMI of 27 kg/m^2, and 5.10 mmol/L (5.07–5.13) and 5.87 mmol/L (5.79–5.96), respectively, for a woman aged 55 years with a BMI of 27 kg/m^2. Fasting glucose levels increased marginally with increasing age by 0.002 mmol/L (0.001–0.003) per year of age in models adjusted for sex and time-varying BMI. In contrast, 2-h glucose levels showed a more pronounced increase over time, with a rise of 0.071 mmol/L (0.067–0.074) per year.

Individual and combined associations of common genetic variants with fasting glucose by age. Significant associations with fasting glucose at age 55 years were observed for 9 of 16 SNPs, with mean per-allele differences

ranging from 0.02 to 0.08 mmol/L (Fig. 1, *left panel*) for the majority of established fasting glucose loci, in line with the earlier report (10). Age-dependent analysis suggested that the association of rs560887 in *G6PC2* became stronger ($P = 0.041$) with advancing age (Fig. 1, *right panel*). No significant differences in associations by age were found for the remainder of fasting glucose loci (Fig. 1, *right panel*). Considering joint associations of the 16 fasting glucose loci, a significant difference of 0.029 mmol/L (95% CI 0.023–0.034) per genetic score point ($P = 2.76 \times 10^{-21}$) was observed in participants at age 55 years, an association that remained constant over time (P value for age interaction = 0.17; Fig. 1, *left* and *right panels*; Fig. 3).

Individual and combined associations of common genetic variants with 2-h glucose by age. Glucose-raising alleles of all five 2-h glucose loci were positively associated with postload glucose levels at age 55 years, with effect sizes that were similar to or larger than those previously reported (11), with variants in *GIPR*, *TCF7L2*, and *ADCY5* reaching conventional levels of statistical significance (Fig. 2, *left panel*). Of five established loci, the association of *TCF7L2* at age 55 years (0.066 mmol/L [95% CI 0.001–0.132]; $P = 0.046$) became significantly stronger with increasing age by 0.012 mmol/L (0.006–0.019) per allele per year (P value for age interaction = 1.1×10^{-4} mmol/L; Fig. 2, *right panel*). Investigating the combined associations of all 2-h-glucose loci risk alleles, 2-h glucose

levels were 0.076 mmol/L (0.047–0.105) higher per genetic score point ($P = 3.1 \times 10^{-7}$); notably, this association became stronger with increasing age by 0.0059 mmol/L (0.0031–0.0087) per genetic score point per year (Fig. 2, *left* and *right panels*; P value for age interaction = 3.0×10^{-5}), resulting in diverging age trajectories by genetic score (Fig. 3).

For both fasting and 2-h glucose sensitivity analysis for the combined effect of all SNPs was performed by calculating both unweighted and weighted genetic scores separately, with both scores yielding very similar results.

Associations of changes in BMI with changes in fasting and 2-h glucose. In models described above, and including age, sex, genotype score, and time-varying BMI, changes in BMI over the study period were associated with increases in 2-h glucose of 0.098 mmol/L (95% CI 0.088–0.108) per kg/m^2 (P value = 3.27×10^{-80}), an effect size that was three times as large compared with that observed for fasting glucose (0.033 mmol/L [0.030–0.037]; P value = 3.92×10^{-77}).

DISCUSSION

The effects of aging on trajectories of fasting compared with 2-h postload glucose differ, with 2-h glucose showing a steeper age-related rise in nondiabetic individuals than fasting glucose (1,3,4). Using prospective, repeated measures
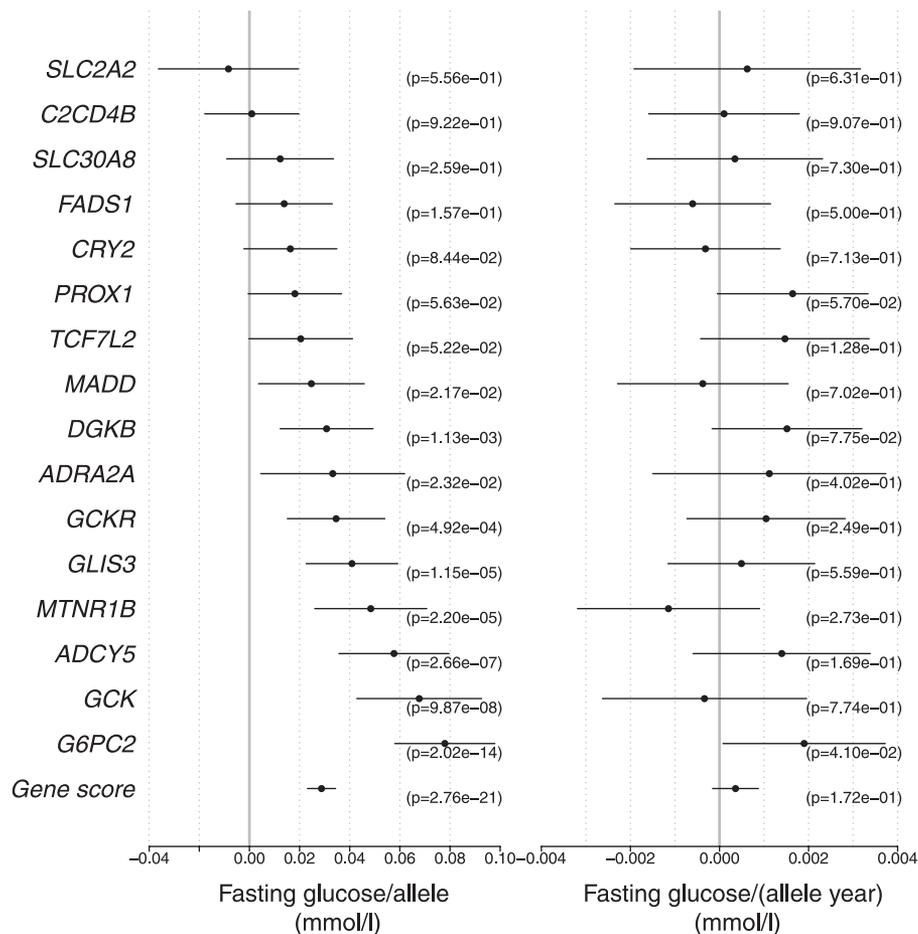

FIG. 1. Effect of 16 selected SNPs on fasting glucose levels. *Left panel*: Mean difference in fasting glucose per risk allele at age 55 years adjusted for BMI (intercept). *Right panel*: Mean increase in fasting glucose per risk allele per year of age, over and above the effect at age 55 years (age-dependent change in effect).
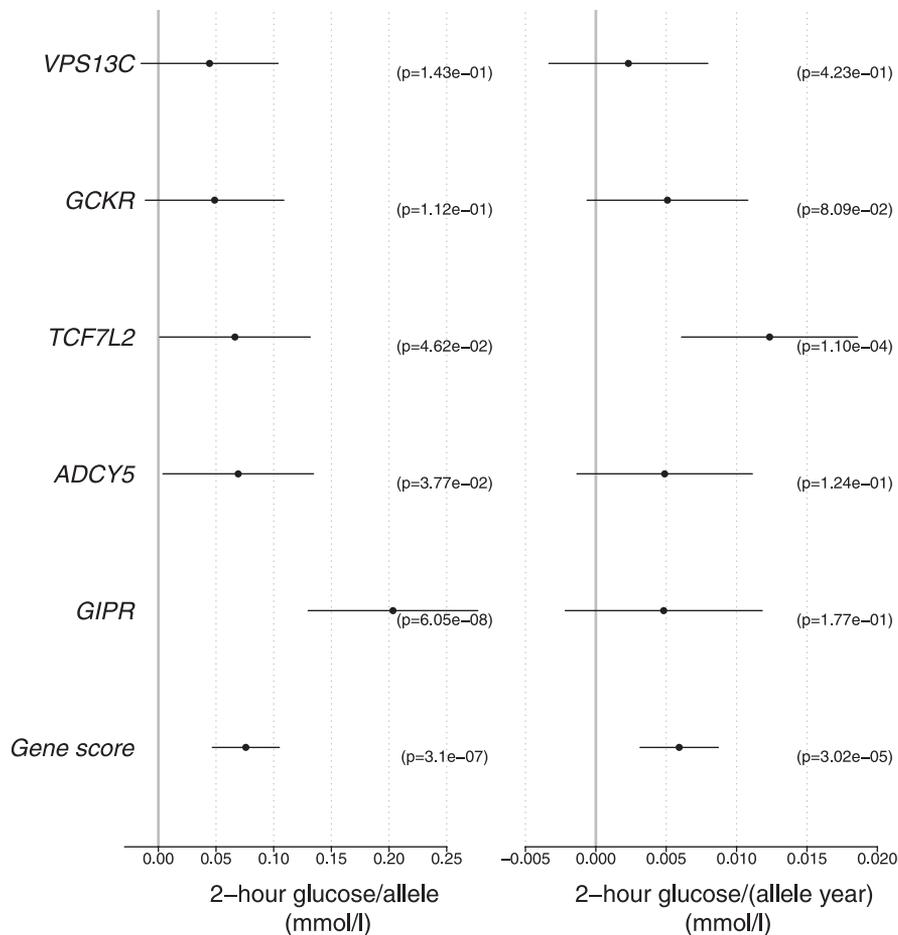
FIG. 2. Effect of five selected SNPs on 2-h glucose levels. *Left panel*: Mean difference in 2-h glucose per risk allele at age 55 years and adjusted for BMI (intercept). *Right panel*: Mean increase in 2-h glucose per risk allele per year of age, over and above the effect at age 55 years (age-dependent change in effect).

from 5,196 nondiabetic participants of the prospective, observational Whitehall II cohort, who were followed for a maximum of 18 years, we demonstrate for the first time that genetic susceptibility for increased levels of 2-h glucose contributes to the steeper age-related rise of this trait.

Of five established 2-h glucose loci, common variation in *TCF7L2* showed a significant effect and the strongest individual effect, with an increase in effect of 0.012 mmol/L per year per glucose-raising allele, which translates into an additional increase in 2-h glucose levels of 0.49 mmol/L when aging from 55 to 75 years and comparing participants carrying both versus no *TCF7L2* risk alleles. *TCF7L2* is the strongest type 2 diabetes gene identified to date, with a per-allele odds ratio of ~1.4. Although the association between variants in *TCF7L2* and type 2 diabetes was first reported in 2006 (15), the exact mechanism by which the identified variants increase type 2 diabetes risk is still debated (16). Results from this study suggest that variants in *TCF7L2* increase type 2 diabetes risk via an age-related effect on postload glucose levels, potentially as a consequence of age-dependent changes in the multiple effects previously reported for *TCF7L2*. These include decreased β-cell mass (17,18), impaired insulin processing or release (17,19,20), impaired incretin signaling in β-cells (17,19,21), decreased glucagon secretion (19), and hepatic insulin resistance (19). Interaction effects of the other four 2-h loci were also positive, but small and nonsignificant, and are thus likely to have had a minor

contribution to the age-related effect of the genetic susceptibility score in comparison with TCF7L2.

Although the effects of risk alleles in or near the 16 loci associated with fasting glucose combined into a genetic susceptibility score did not significantly change with age and showed parallel glucose trajectories throughout middle age by genetic score group, one of the fasting glucose loci, *G6PC2*, showed a significant increase in its effect with age. However, the magnitude of the time-dependent effect was comparatively small (0.002 mmol/L per year per allele), amounting to an additional increase in fasting glucose levels of 0.08 mmol/L when aging from 55 to 75 years and comparing participants carrying both versus no *G6PC2* risk alleles. Bonferroni correction for multiple testing of 23 "independent" tests (including tests for all fasting [$n = 16$] and 2-h SNPs [$n = 5$] plus tests for each genetic score [$n = 2$]) resulted in a nonsignificant interaction term for the age-dependent effect of *G6PC2* on fasting glucose levels. In contrast, the corrected age interactions observed for *TCF7L2* ($P_{corrected} = 2.5 \times 10^{-3}$) and the 2-h glucose genetic susceptibility score ($P_{corrected} = 3.2 \times 10^{-4}$) remained significant. Although it is arguable whether individual SNPs and the genetic scores constitute independent tests, we counted each of the tests separately to apply a more stringent statistical correction and be conservative in our interpretation. However, using less stringent criteria did not alter our results or conclusions.
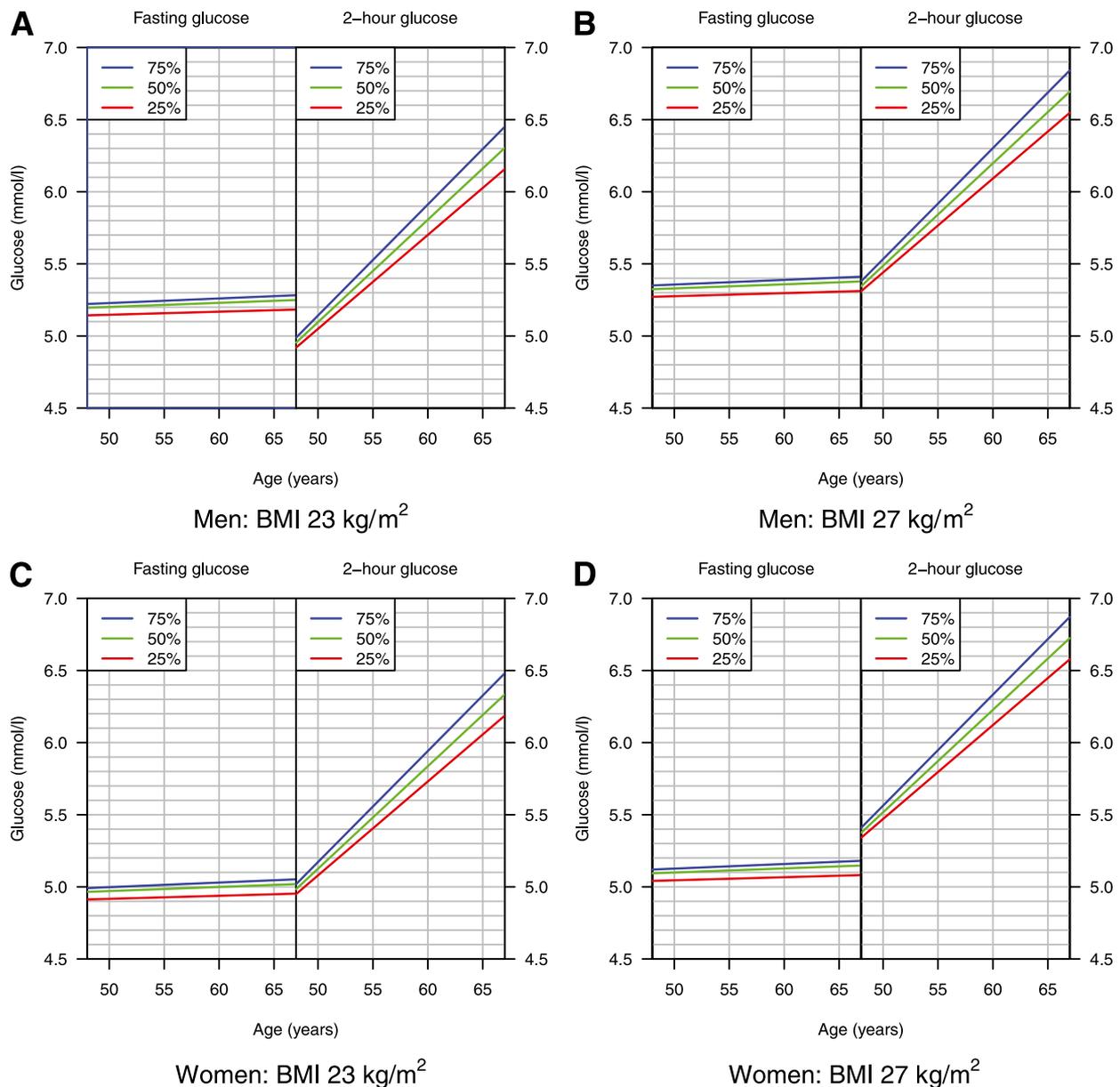
FIG. 3. Estimated mean fasting and 2-h glucose levels for the 25th (red), 50th (green), and 75th (blue) percentiles of the respective fasting (*left panels*) or 2-h (*right panels*) genetic scores for men with a BMI of 23 kg/m² (*A*), men with a BMI of 27 kg/m² (*B*), women with a BMI of 23 kg/m² (*C*), and women with a BMI of 27 kg/m² (*D*). Values of the score are 17, 19, and 20 for fasting glucose and 3, 4, and 5 for 2-h glucose for the 25th, 50th, and 75th percentiles, respectively.

Main effect sizes of loci emerging from meta-analyses of GWASs of glycemic traits are small, and large sample sizes are required to identify effects in individual replication studies such as Whitehall II, as evidenced by the fact that we failed to observe significant main associations for some of the weaker established SNPs despite effect sizes that are comparable to previous meta-analyses. This study is therefore also likely to be underpowered to observe significant interactions with age for small effects; however, the clinical significance of identifying interactions smaller than those observed in this study may be questionable. For example, the effect of a difference in one unit of the genetic score for fasting or 2-h glucose observed in this study is equivalent to the effect of a 1 kg/m² difference in BMI or 2 additional years of age in the case of 2-h glucose; in comparison, the age-dependent effect of the 2-h glucose

genetic score amounts to an additional 0.06 kg/m² or 1.6 months of aging per year. Future studies of similar size are warranted to replicate our findings in an independent setting, although few studies have prospective data with repeated OGTTs over a follow-up of 18 years available.

The observation that fasting glucose levels do not show the steep age-related rise of postload glucose levels may point toward a smaller influence of environmental factors on this trait compared with 2-h glucose levels, with a number of previous studies showing a larger nongenetic component to variance in 2-h glucose levels compared with fasting glucose (22,23), although it is important to note that the magnitude of genetic and nongenetic contributions to fasting and 2-h glucose levels can vary by the population studied. However, in support of this, the greater number of loci identified for fasting versus 2-h

glucose levels also suggests a greater genetic component, although the somewhat smaller GWAS sample size and the greater measurement error and SD of 2-h glucose may also contribute (10,11). Taken together with the fact that large differences in fasting glucose according to presence or absence of fasting glucose-raising alleles have been demonstrated as early as young childhood for the earliest published fasting glucose loci (24), this suggests a model in which genetic influences on fasting glucose levels are evident early in life and contribute to long-term differences in glucose trajectories that remain constant with increasing age. Few studies (7,25,26) have published results based on longitudinal data. These reported effects of rs1799884 in *GCK* on changes in fasting glucose cross-sectionally (25), without evidence of differences in effects by age or over time (26). Lyssenko et al. (7) also showed that carriers of the fasting glucose–raising G allele in *MTNR1B* (rs10830963) had higher glucose levels and lower insulin secretion at baseline as well as 7 years later in the Botnia study. Likewise, during 24-years of follow-up in the Malmö Preventive Project, glucose levels in GG homozygotes rose by only 0.05 mmol/L, with similar small differences in the other genotype groups, emphasizing the stable trajectories of fasting glucose with age (7).

The key environmental factors contributing to the rise in 2-h glucose with age are unclear, but previous studies have suggested that increases in sedentary behavior and adiposity may be key determinants (27). Our results show an effect of changes in BMI over the study period on 2-h glucose that was three times as large compared with that observed for fasting glucose, in line with a stronger influence of age-related lifestyle behavioral factors on post-challenge glucose. However, in the current study the effects of genetic variants on changes in 2-h glucose over time were not explained by changes in BMI over the same time, although other measures of adiposity may be more important but have not yet been investigated.

The results presented here are the first to show that common genetic variants may contribute to the age-related rise in postload glucose in nondiabetic individuals. As for the example of *TCF7L2*, effects could be mediated by defects in β-cell function and changes in insulin secretion, rather than influences on insulin sensitivity because the majority of studies investigating effects of *TCF7L2* variants report effects on insulin secretion/processing, with the few studies showing defects associated with insulin action yet to be replicated (16). An insulin secretory defect leading to a deterioration of β-cell function through hyperglycemia and β-cell glucotoxicity may contribute to the age-dependent increase in 2-h glucose levels observed in this study.

Genetic variants included in this study were recently discovered based on meta-analyses of cross-sectional GWASs. Using multilevel models, including prospective, observational data from 5,196 participants and 13,141 OGTTs, this is the first study to investigate differences in the effects of these recently identified common genetic variants on long-term glucose levels in nondiabetic individuals. Our results suggest that participants' age may be an important contributor to the observed heterogeneity in effects between different studies included in earlier meta-analyses, particularly for 2-h glucose, and that age-stratified analyses may be more appropriate than investigating average age-adjusted effects.

We raise caution against using our results for the prediction of individual glucose levels. The residual intra- and interindividual variation in fasting and 2-h glucose after accounting for the genetic effects and their interaction with age is still considerable. Consequently, any individual glucose prediction based solely on genetic and age information will fall short of predictions based on models that account for a wider set of established determinants. Also, results from this study of white, London-based civil servants are not necessarily representative of the general population. Although effect estimates of genetic variants were similar in this study compared with previous studies, lifestyle and associated behaviors, including factors associated with aging, are likely to be different in this occupational cohort, which on average is healthier and socially advantaged compared with the general population (12). We observed some differences when comparing the characteristics of participants attending study phase 7 (when DNA was collected) who were included versus excluded in this study. However, to bias our results, these differences would have to be differential with regard to genotype, which is unlikely to be the case. In addition, given our exclusion criteria (nonfasting status, prevalent diabetes) some differences between included and excluded participants are to be expected. Our analysis includes individuals who did not have glucose measured at all time points, and this assumes that missing occurs at random. Again, we have no reason to believe that individuals were selectively lost to follow-up based on their genotype.

Our observation of significant differences in effects of glycemic loci with age suggest that the same may be true for any number of variants discovered in cross-sectional GWASs. Whether the time-dependent effect of any variant has an important influence on the time course of the phenotype it is associated with will be dependent upon the magnitude of the effect and its potential modification by other risk factors. In addition to influencing the time course of phenotypes, time-dependent effects of variants could also have clinical relevance, as is suggested here for *TCF7L2*, with the time-dependent increases in 2-h glucose observed with this variant potentially contributing to its association with increased type 2 diabetes risk.

Although individual effects of common genetic loci included in this study are small, differences in glucose levels between individuals at low and high genetic risk amount to ~1 SD when considering the combined effects of all known loci in a weighted score using data in our own study; this result is identical to that reported in the MAGIC study of adults (10). In addition, effects of fasting glucose loci have been shown to be evident from early childhood, and, hence, differences in glucose levels and associated metabolic consequences appear to start at an early age. The current study extends these findings and shows that in addition to existing differences in average glycemia between individuals at high and low genetic risk at a particular age, differences attributed to common genetic variation may become more pronounced at higher ages for 2-h glucose.

In conclusion, our results suggest that associations between common genetic variants and fasting glucose are constant over time, in line with stable age trajectories of fasting glucose in nondiabetic individuals. We propose a model in which an individual's fasting glucose set point is determined early in life by combinations of genetic variants with age-independent effects, resulting in relatively stable trajectories of fasting glucose over the life course. In contrast, genetic effects on 2-h glucose appear to depend on age, such that differences in 2-h glucose per additional

risk allele increase with advancing age, particularly in carriers of risk alleles in *TCF7L2*. Our findings suggest that the effects of age or related environmental factors need to be taken into account when studying genetic influences on 2-h glucose levels and that differences in participants' ages may contribute to heterogeneity in effects of postload glucose loci between studies.

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