The interplay of lifestyle and genetic susceptibility in Type 2 diabetes risk

Paul W Franks†1,2,3 & Dmitry Shungin1,3

Practice Points

- Current risk algorithms containing information on common genetic variation are of little clinical utility owing to their poor predictive ability.

- It is likely that common genetic variants convey different levels of risk for Type 2 diabetes depending on the environmental risk factors to which a person is exposed.

- Where genetic risk varies across environmental contexts, it may be possible to harness this information to improve the performance of genetic risk algorithms.

- At present, the most effective risk algorithms are those that do not include genetic information. However, the inclusion of information on first-degree family history of diabetes, which to some extent reflects a person’s genetic background, does meaningfully increase the predictive ability of many diabetes risk algorithms.

- Human genetics research is moving at a very rapid pace. The continuing discovery of novel genetic risk variants for Type 2 diabetes should be anticipated. The implementation of this information into prediction algorithms may further enhance the clinical relevance of these tools.

- Genetic information may also prove valuable for the delineation of the molecular mechanisms that cause Type 2 diabetes and reveal opportunities for the development of drug targets to prevent or treat the disease.

SUMMARY Type 2 diabetes results from the complex interplay of adverse lifestyle exposures and genetic predisposition. Accordingly, genetic information might one day facilitate personalized medical interventions for diabetes prevention, thus minimizing treatment costs, reducing patient exposure to ineffective therapies and improving patient adherence to treatment recommendations and their prognosis. Here, we briefly overview the roles that obesity, physical activity and dietary factors play in Type 2 diabetes; define common approaches used to discover genetic risk factors and gene–lifestyle interactions; provide relevant examples of gene–lifestyle interactions; and speculate on the application of genetics to the prediction, prevention and treatment of diabetes.

†Author for correspondence: Tel.: +46 4039 1149; Fax: +46 4039 1222; paul.franks@med.lu.se
Type 2 diabetes is a disease of relative insulin deficiency. Persons with well-managed diabetes can live long and otherwise healthy lives, but when management fails, diabetes has truly awful consequences such as loss of limbs, blindness, kidney failure and damage to the heart and vessels; tragically, around 75% of people with diabetes eventually die from cardiovascular disease [1,2].

Diabetes takes a grip when the pancreatic β cells are no longer able to secrete sufficient volumes of insulin to maintain whole-body glucose homeostasis. Although an individual with failing β cells can transition quickly from impaired glucose regulation (sometimes referred to as prediabetes) to full-blown diabetes [3], the decline in β-cell function and glucose uptake that precedes diabetes tends to gradually manifest over many years, with an accelerated deterioration in glucose control in the later stages [4]. The factors that contribute to this decline are numerous, but often involve obesogenic lifestyle behaviors such as physical inactivity and dietary excess. Indeed, at the point of diagnosis, approximately 80% of people with Type 2 diabetes are estimated to be obese [5,6].

Randomized controlled trials of intensive lifestyle modification or drug monotherapy that result in weight loss substantially reduce the progression to diabetes in high-risk individuals [7,8] and bariatric surgery in people who are morbidly obese and diabetic can result in almost immediate remission from the disease [9]. Nevertheless, diabetes is by no means an inevitable consequence of obesity, as many people who are obese never develop the disease, suggesting the involvement of one or more catalysts present in some people but not in others, that are triggered by obesity or its correlates. The relatively high familial risk of diabetes [10–12] strongly suggests that those catalysts may be genetic in nature and that Type 2 diabetes is therefore the consequence of complex interactions between genetic and lifestyle factors.

In this article we discuss the relative contributions of obesity, genetics and lifestyle factors to the etiology of Type 2 diabetes. We then examine selected studies that implicate gene–lifestyle interactions in the disease and ask how valuable knowledge of gene–lifestyle interactions is likely to be for the prediction and prevention of diabetes.

**Obesity & Type 2 diabetes**

One of the major modifiable risk factors for Type 2 diabetes is obesity, which is conventionally defined as a BMI of at least 30 kg/m². Although many obese people never develop diabetes, of those with the disease, most are obese at the time of diagnosis. Largely because BMI is easily measured, it is widely used in clinical research and practice to quantify a person’s level of overweight or obesity. However, BMI is a proxy for several components of body composition, such as adipose mass, subtype and distribution, skeletal muscle mass, bone mass and organ size. Because BMI is not a perfect correlate of these traits, two people with the same BMI may have radically different body compositions [13] and underlying metabolic risk profiles [14]. Nevertheless, in diabetes research, where we are often interested in adipose mass and distribution, the correlation between BMI and these traits is sufficiently strong [15] to permit meaningful inferences about their relationships with diabetes risk to be made using BMI as a proxy measure of adiposity.

There are numerous mechanisms through which obesity causes Type 2 diabetes, many of which include insulin resistance brought about by factors that detrimentally impact the sensitivity of the body’s cells to insulin, such as lipid accumulation in and around myocytes, adipocyte hypertrophy, macrophage infiltration of adipocytes and cellular inflammation. These processes are augmented by elevations in adipocyte-derived hormones such as resistin, retinol binding protein 4, TNF-α and IL-6 and a diminution in adiponectin concentrations [16]. Obesity is also highly heritable [17] and has a complex genetic and epigenetic [18] basis that is only partially defined at present [19].

**Lifestyle factors & Type 2 diabetes**

As obesity is a consequence of chronic positive energy balance, there is a real opportunity to impact diabetes risk through programs of intensive lifestyle modification that lead to weight loss. Indeed, numerous randomized clinical trials have clearly shown that diet and exercise interventions that result in weight loss can substantially reduce the progression to Type 2 diabetes when compared against the incidence in a normal care control group [7,8]. Studies from the 1980s of exercise training in Swedish men with or without Type 2 diabetes provided some of the first evidence that exercise can transiently normalize blood glucose concentrations even in persons with deficient pancreatic β cells [20]. The reasons why exercise is so effective at restoring glucose homeostasis is because the mechanisms
for glucose disposal during exercise are largely independent of those by which insulin operates [21]. Dietary factors, on the other hand, impact both insulin- and noninsulin-mediated glucose disposal pathways [22]. Thus, dietary interventions may have a greater capacity to prevent diabetes than exercise intervention, although a recent synthesis of clinical trial evidence suggests that the combination of diet and exercise regimes are probably required for diabetes risk reduction, with neither proving tremendously efficacious when acted on alone [23].

**Approaches to discovering the genetic basis to Type 2 diabetes**

The initial methods that were used to identify genetic loci influencing Type 2 diabetes risk included family-based linkage studies and studies of biologic candidate genes. The linkage approach involves studying the segregation of a disease or trait within family pedigrees that have been genotyped for a panel of conventionally ~500 microsatellite markers spaced equally across the genome. In the event that the trait and genetic markers co-segregated and a linkage signal emerged, the respective genomic region would then be sequenced in the hope that the disease-causing locus could be mapped. Although linkage studies proved successful for the detection of rare, highly penetrant disease-causing mutations, they failed almost entirely for the disease-causing loci could be mapped. The approach completely contrasts the biologic candidate gene approach in that it is agnostic to prior knowledge about the role of a gene in a specific disease.

The GWAS method is essentially quite simple, beginning with genotyping hundreds of thousands or even millions of gene variants in very large cohort collections (sometimes in excess of 100,000 samples), with the imputation of 2–3 million more variants per individual. The associations between each of these gene variants and the trait of interest are then tested [28]. Because the multiple hypothesis testing burden is enormous, GWAS apply very stringent significance thresholds (p < 1 × 10^-8) in order to determine whether a variant is reliably associated with the disease trait; the level of statistical significance used in GWAS is roughly equivalent to a p-value below 0.01 after experiment-wide Bonferroni correction.

Although progress in the discovery of Type 2 diabetes predisposing loci was painfully slow for many years, the discovery of TCF7L2 in 2006 [24] and the subsequent emergence of the paradigm-leaping GWAS approach transformed this situation. Prior to 2006, only two adequately replicated Type 2 diabetes loci (PPARG Pro12Ala [29] and KCNJ11 E23K [30]) had been discovered in roughly a decade of single nucleotide polymorphism (SNP)-based genetic research. However, since 2006, SNPs in almost 40 loci have been robustly replicated, many emerging from GWAS experiments [31]. Nevertheless, none of the discovered loci have conveyed particularly large risk effects and the aggregate predictive ability of all confirmed Type 2 diabetes loci remains fairly modest [31,32]. It is possible that the remaining variability in a person’s heritable risk of diabetes can be explained in part by rare genetic variants (with an allele frequency less than 1% in a population) that are inadequately detected by existing GWAS techniques [28,33]. Rare genetic variants may have large effect sizes and thus may explain much of the ‘missing heritability’ that GWAS failed to detect. Rapidly emerging...
next-generation sequencing technologies, which allow high-resolution characterization of the nuclear genome, may shed light on the genetic basis of Type 2 diabetes and may also be of value when studying the role of gene–environment (or treatment) interactions.

Genetic information can also be used to infer casual relationships between lifestyle factors and diseases such as Type 2 diabetes in observational data using an approach termed Mendelian randomization [34]. Because alleles are randomly assorted during meiosis in diploid organisms, rendering associations between SNPs and phenotypes free from many forms of confounding common to nongenetic exposures, this characteristic can be leveraged to quantify the presence and magnitude of relationships between biologic traits that are associated with each other as well as with the index SNP. A recent example of how this approach has been applied to metabolic traits involved the examination of BMI, C-reactive protein levels and Type 2 diabetes [35,36]. The authors of those studies convincingly showed that the relationship between C-reactive protein and BMI is likely to be driven by BMI and that C-reactive protein is unlikely to cause Type 2 diabetes, which is all but impossible to determine using nongenetic observational data alone.

Approaches to studying the interaction of genetic & lifestyle factors in Type 2 diabetes etiology

Lifestyle interventions vary in complexity, emphasis, cost and effectiveness. Two of the most successful diabetes prevention randomized clinical trials, deploying almost identical programs of behavioral modification for weight loss, are the Finnish Diabetes Prevention Study and the Diabetes Prevention Program [7,8]. In both studies, emphasis was placed on 7% body weight reduction by increased habitual physical activity and structured exercise training, decreased total calorie intake (e.g., by reducing dietary fat and sugar intake) and improved dietary quality (e.g., by increasing consumption of fresh fruit and vegetables and fiber-rich foods). A total of 16 instructor-led classes were delivered to each participant to enhance the effectiveness of the intervention and to help participants achieve these goals. Since the publication of the main findings from the Finnish Diabetes Prevention Study and the Diabetes Prevention Program, numerous other studies have followed, some of which have translated the core protocol into the primary care setting with some success [37]. Nevertheless, a universal aspect of lifestyle intervention studies is that responses to such interventions differ markedly from one person to the next. Although adherence to the intervention is an important source of variation, even when this is accounted for, some variance in response persists [38]. These findings, in combination with family-based exercise intervention studies, where responses to interventions correlate more strongly between family members than between members of different families [39], indicate that genetic factors may underlie an individual’s response to lifestyle interventions. If this is true and the specific genetic variants that predict an individual’s response to intervention can be localized, it might be possible to use this information to aid the prevention and treatment of Type 2 diabetes.

The process of translating the three different genetics approaches described above (linkage, biologic candidate gene and GWAS) to the investigation of gene–lifestyle interactions has met with limited success so far. The majority of biological candidate gene studies and linkage studies that have explored gene–lifestyle interaction effects have yielded results that remain to be adequately replicated. The most promising example of an interaction involving a biologic candidate gene is for the Pro12Ala variant at the PPARG gene [40]. Several studies have reported on interactions between this variant and dietary fat intake on insulin resistance or obesity. The first study reporting on this effect was published almost a decade ago [41] and showed that in a small cohort of people from the UK (n = 592), the Pro12Ala variant modified the relationships of polyunsaturated to saturated dietary fat intake with obesity and insulin resistance. A study from the US also reported similar interaction effects, but in that example the dietary exposure was monounsaturated fats [42]. Since then, more than 20 follow-up studies have been reported on related topics, but the extent to which the initial observation can be said to have been replicated needs to be considered in the context of the variability in study designs, the specific nature of the hypothesis tests and the nature of the reported interaction effects, all of which vary to some degree across the follow-up studies. Indeed, a recent attempt to retrospectively meta-analyze the published literature on this topic [43] concluded that because
of publication and measurement biases and heterogeneous study designs and approaches to reporting data, no meaningful conclusion could be made by pooling published studies of interaction.

An alternative approach to testing hypotheses of gene–lifestyle interactions is to carry forward top ranking loci discovered in GWAS and examine whether they modify the relationships of lifestyle exposures with Type 2 diabetes or related traits. As we describe below, several studies that have taken this approach have been published. For example, Li et al. observed statistically robust interactions between a genetic risk score comprised of 12 GWAS-derived obesity predisposing loci and physical activity on the risk of obesity in a large cohort of British adults [44]. However, this approach also has its limitations, not least that the methods for conducting conventional GWAS experiments are probably biased towards the detection of loci that do not interact with other factors. This is because such studies typically utilize the probability statistic (p-value) to rank loci, which is influenced by a combination of factors including the heterogeneity of the effect estimate; because interactions increase the heterogeneity of the component marginal effects, genetic loci that express their effects via interactions will tend to be ranked lower in GWAS experiments than those that do not. Although methods exist to overcome these limitations, they are not widely implemented at this time, as they require the incorporation of interaction terms (rather than just main effects) into the models, which is a relatively time-consuming process.

Examples of gene–lifestyle interactions in Type 2 diabetes & related traits
The largest and most comprehensive study testing GWAS defined loci for interactions with lifestyle factors in Type 2 diabetes involved around 16,000 initially nondiabetic Swedish adults who were followed for a median duration of 25 years during which time approximately 2000 incidences of Type 2 diabetes occurred [45]. Each of the 17 confirmed Type 2 diabetes gene variants included in the study were tested for interaction with the baseline physical activity level. After correction for multiple hypothesis testing, there was only one interaction effect that remained statistically significant. In that example, physical activity was strongly protective of incident Type 2 diabetes in people carrying neither copy of the risk allele at the HNF1B rs4430796 variant. However, in persons with one or both copies of the risk allele at this locus, the protective effects of physical activity were substantially diminished.

Elsewhere, Jablonski et al. studied the interaction of roughly 1590 SNPs (tagging 40 loci) with placebo, metformin or lifestyle modification interventions on Type 2 diabetes incidence in the Diabetes Prevention Program [46]. The selected loci included biologic candidate genes as well as variants discovered in recent GWASs. Overall, there was no convincing evidence of interactions between gene variants and the lifestyle intervention, with the most convincing results being an interaction between a variant in SLC47A1 (encoding the OCT1 metformin transporter) and metformin treatment.

One of the most exciting examples of a gene–lifestyle interaction reported to date involves a gene variant at the FTO locus (rs9939609). FTO was first implicated in Type 2 diabetes in 2007 as part of the Wellcome Trust’s Case Control Consortium study [47]. The authors found that the rs9939609 variant raised Type 2 diabetes risk, but that this effect was mediated by obesity. In other words, by virtue of an association between the minor A allele at the rs9939609 variant and obesity risk, Type 2 diabetes risk was also elevated. The initial study to report evidence of gene–physical activity interactions at this locus was conducted in a population-based cohort of approximately 5500 Danish adults from the Inter99 Study [48]. The authors found that in physically inactive individuals, BMI differed by around 2 kg/m² units between the high (AA) and low (TT) risk homozygotes. However, in people reporting moderate to high levels of physical activity, the magnitude of this genetic effect was reduced to approximately 0.5 kg/m², which was reflected by a statistically significant gene–physical activity interaction. Several other studies published since this original report have yielded variable results. A study in around 700 Amish adults [49] reported a statistically significant interaction for another FTO SNP that is in low linkage disequilibrium with the variant reported in the Danish study. Although the study was relatively small, it included objective physical activity measures and the interaction effect was generally consistent in direction and magnitude with the Danish findings. Clinical trial data from the Diabetes Prevention Program also support the presence of gene–lifestyle interactions on 1-year changes in subcutaneous
adipose mass [50], but several other large epidemiological studies and small clinical trials were unable to confirm these results. Because few studies of gene–lifestyle interaction are, on an individual basis, likely to be adequately powered to detect effects, a large consortia-based effort was undertaken in which all published and unpublished data pertinent to this hypothesis (n ~ 240,000 individual observations) were collated and analyzed using a standardized analytical approach [KiepeLainen T, Pers. Comm.]. The results of the study were pooled using meta-analysis and confirmed the initial reports of interaction. Nevertheless, the interaction effect sizes were considerably smaller than those reported in the original studies, which is possibly owing to the so-called ‘winner’s curse’. Very recently, the CHARGE consortium reported findings on gene–nutrient interactions and wholegrain food intake on glucose and insulin levels. The study consisted of roughly 48,000 individual observations from 14 cohorts. The strongest evidence for interaction was for the putatively functional rs780094 variant at GCKR [51], whereby each copy of the Type 2 diabetes-associated allele diminished the protective effects of wholegrain food intake on fasting insulin levels by roughly half.

How might information on gene–lifestyle interactions aid the prediction & prevention of Type 2 diabetes?

Scientists and practitioners have long since been aware of the considerable interindividual differences in susceptibility to specific diabetogenic exposures or responses to antidiabetic treatments. Many have recognized that these differences may be related to individual genetic variation, but to identify the specific variants underlying these interactions has proven very difficult. Despite this, there is widespread optimism that genetics has an important role to play in personalized medical therapy [52]. Proof of this concept already exists for sulfonylurea tablet therapy as a replacement for daily insulin injections in diabetic carriers of MODY2 mutations [53] and in African–Americans with heart failure for which the US FDA specifically approved the use of the drug BiDiil®, which it does not for other ethnic groups [101].

The use of genetics to tailor medical treatments and preventive interventions in other scenarios will require adequate replication of results from studies of gene–treatment interactions. These examples will not only require extensive replication, but will also need to convey sufficiently large effects, such that the inclusion of genetic information into prediction algorithms out-performs nongenetic risk algorithms. Despite these hurdles, it seems quite possible that genetics will find its way into prevention and treatment paradigms for Type 2 diabetes before too long, perhaps as part of more complex screening approaches that combine other demographic, biologic and behavioral information to identify individuals who are likely to respond well or poorly to specific antidiabetic therapies.

Conclusion

As we explained earlier, genetic and lifestyle factors do not act independently on Type 2 diabetes risk. Our understanding of how genetic and lifestyle risk factors combine to influence Type 2 diabetes risk is far from perfect, but we can at least envisage a framework within which these factors operate, allowing us to conceive research paradigms that should help define in fine detail the specific components of these interactions, the manner in which the interactions manifest and the strategies that we will need to adopt to utilize this information in a way where it helps prevent the development or limit the consequences of Type 2 diabetes. If the evidence base becomes strong enough to warrant the inclusion of information on interactions of genetic and environmental factors into prediction algorithms for Type 2 diabetes, this may facilitate the tailoring of medical therapies to the individual, thus minimizing treatment costs and exposure to ineffective therapies and improving patient treatment compliance and treatment outcomes.

Future perspective

Type 2 diabetes is a preventable disease. The major modifiable risk factors are known and clinical trials have shown that intervening on these risk factors substantially reduces the risk of Type 2 diabetes. However, despite the general success of these studies, a ‘one size fits all’ intervention is suboptimal in several senses, not least from the point of view of the patient’s welfare and the economic burden created by ineffective treatments. It is conceivable that genetic information might help guide the development of personalized medical interventions for diabetes prevention, thus minimizing treatment costs, reducing the extent to which patients are
exposed to ineffective therapies and improving patient motivation and treatment outcomes. In the past 4 years, personal genome testing kits have become widely available, a trend that is almost certainly set to continue. Nevertheless, evidence to support the application of genome profiling for the prediction, prevention or treatment of Type 2 diabetes is generally lacking. In the next 5–10 years, we should expect to see the publication of well-designed scientific studies that provide reliable data on the identities of genetic risk factors that modify a person’s response to antidiabetic interventions. The availability of such information will help guide the development of personal genome testing kits, which may aid the optimization of diabetes prevention and care.

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Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest


- One of the first studies to illustrate the substantial burden of cardiovascular mortality in people with Type 2 diabetes. The study’s findings prompted re-evaluation of the way people with diabetes are treated for cardiovascular risk factors.


3 Mason CC, Hanson RL, Knowler WC: Progression to Type 2 diabetes characterized by moderate then rapid glucose increases. *Diabetes* 56(8), 2054–2061 (2007).


- Published around the time of two major clinical trials showing that intensive lifestyle modification can markedly delay the onset of Type 2 diabetes in high-risk persons. Thus, although the study was observational, it provided important evidence supporting lifestyle modification for diabetes prevention.


- Major randomized clinical trial of intensive lifestyle modification versus control intervention that showed that weight loss through lifestyle modification reduces the 3-year risk of developing diabetes by 58% compared with control intervention.


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- Demonstrates, amongst other things, the remarkable effects bariatric surgery can have on Type 2 diabetes, where remission from the disease is frequently observed immediately after surgery.


- One of the first studies to report heritability estimates for Type 2 diabetes in twins from Denmark.


- Describes a subpopulation of morbidly obese individuals who apparently evade the adverse metabolic consequences frequently seen in obese persons. Many have since sought to identify the specific mechanisms that enable these persons to remain disease free, in the hope that this information might be harnessed and applied to the remainder of the obese population to enhance their health.


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First study to report on the interaction between the PPARG Pro12Ala variant and dietary fat intake in relation to insulin levels and BMI. Several studies provided varying levels of replication for these findings.


Study providing additional evidence that dietary fat intake modifies the association between the Pro12Ala variant at PPARG and body mass.

Palla L, Higgins JP, Wareham NJ, Sharp SJ: One of the largest and most comprehensive studies reported to date. The study showed that a variant at the HNF1B gene may reduce the beneficial effects of physical activity on diabetes risk.


Most comprehensive investigation of genetic risk factors for Type 2 diabetes within the context of a clinical trial. The study confirmed that a variant at the gene encoding the OCT1 transporter modifies the effect of metformin treatment on diabetes incidence.


One of three studies to simultaneously report the discovery of FTO as an obesity-predisposing locus in humans. FTO harbors the most strongly associated common risk allele for obesity.


One of the most promising examples of gene–lifestyle interactions published to date. The study showed that physical activity may attenuate the genetic risk conveyed by an FTO SNP. Subsequent studies have confirmed this interaction effect.

Largest study of gene–nutrient interactions on quantitative diabetes traits reported to date. The study showed evidence of interaction between a GCKR variant and dietary wholegrain intake, whereby the protective effect of wholegrains was substantially diminished in carriers of the diabetes-predisposing allele at this GCKR SNP.


Website