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REVIEW

Do gene–environment interactions have implications for the precision prevention of type 2 diabetes?

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Abstract

The past decades have seen a rapid global rise in the incidence of type 2 diabetes. This surge has been driven by diabetogenic environmental changes that may act together with a genetic predisposition to type 2 diabetes. It is possible that there is a synergistic gene–environment interaction, where the effects of the diabetogenic environment depend on the genetic predisposition to type 2 diabetes. Randomised trials have shown that it is possible to delay, or even prevent the development of type 2 diabetes in individuals at elevated risk through behavioural modification, focusing on weight loss, physical activity and diet. There is wide heterogeneity between individuals regarding the effectiveness of these interventions, which could, in part, be due to genetic differences. However, the studies of gene–environment interactions performed thus far suggest that behavioural modifications appear equally effective in reducing the incidence of type 2 diabetes from the stage of impaired glucose tolerance, regardless of the known underlying genetic predisposition. Recent studies suggest that there may be several subtypes of type 2 diabetes, which give new opportunities for gaining insight into gene–environment interactions. At present, the role of gene–environment interactions in the development of type 2 diabetes remains unclear. With many puzzle pieces missing in the general picture of type 2 diabetes development, the available evidence of gene–environment interactions is not ready for translation to individualised type 2 diabetes prevention based on genetic profiling.

Keywords Diet · Environment · Gene–environment interaction · Genetics · Lifestyle · Obesity · Physical activity · Precision medicine · Review · Type 2 diabetes

Abbreviation
GWAS Genome-wide association study

Introduction

Type 2 diabetes is a common chronic disease affecting more than 420 million people worldwide [1]. The prevalence of type 2 diabetes has more than doubled since the early 2000s and continues to increase at an alarming rate [1]. The long-term life-threatening complications of type 2 diabetes are a major burden on individuals and societies as a whole. In light of today's challenges to find sustained effective treatments, focusing on prevention is essential.

Both genetic and environmental factors are involved in the aetiology of type 2 diabetes. Studies in twins and families suggest that type 2 diabetes is strongly heritable [2, 3], but the recent rapid changes in type 2 diabetes incidence emphasise a key role of environmental changes. It has been proposed that type 2 diabetes may develop as a result of interactions between genetic and environmental factors, where the effect of environmental risk factors is enhanced by acting together with genetic predisposition to type 2 diabetes.

Type 2 diabetes is a heterogeneous disease. Recent studies have identified several putative subtypes of type 2 diabetes with different pathophysiologies, clinical manifestations and prognoses [4–6]. These findings give new opportunities for gaining insight into the development of type 2 diabetes, including possible gene–environment interactions that may

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Implications of type 2 diabetes subtypes for precision prevention

Subtypes of type 2 diabetes Studies partitioning individuals into distinct clusters based on key phenotypic characteristics have identified different subphenotypes of type 2 diabetes risk and subtypes of type 2 diabetes that may differ in pathophysiology, clinical manifestation and prognosis [4-6].

Implications for precision prevention It is possible that the type 2 diabetes subtypes may differ in genetic, behavioural and environmental aetiology. If so, their response to preventive interventions may also differ. The ability to predict these differences could help target and tailor early interventions to individuals who would benefit the most, opening avenues for personalised lifestyle interventions.

Role of genetic information Genetic loci that have been identified as being associated with type 2 diabetes subtypes may, in the future, be used to classify individuals into subgroups at an early stage. This could make it possible to choose the best-suited preventive intervention for each individual, when combined with information from other predictive metrics.

Translational challenges For translation into personalised interventions, it must be possible for the identified genetic and other predictive markers to be assessed and behavioural factors targeted before the emergence of the disease. In addition, the personalised interventions must eventually be shown to reduce the risk of later development of the disease more effectively than a generalised intervention.

be identifiable before emergence of the disease. Identification of genetic differences that together with particular environmental or behavioural factors associate with type 2 diabetes subtypes before the disease is manifest would also raise the possibility that there can be subtype-specific preventive interventions (see Text box: Implications of type 2 diabetes subtypes for precision prevention).

In the present review, we will first summarise the current evidence of type 2 diabetes-associated genetic factors and environmental factors, and their interactions in the development of type 2 diabetes. We will focus particularly on obesity, physical activity and dietary habits as major modifiable risk factors of type 2 diabetes, to which we refer broadly as behavioural factors. Considering that obesity is the main risk factor for type 2 diabetes and, in part, a product of these behaviours, the role of gene–environment interactions in obesity will be an integral part of this review. We will then examine the implications of gene–environment interactions for the prevention of type 2 diabetes and, finally, outline the challenges that lie ahead for using this information to prevent type 2 diabetes.

Genetic risk factors of type 2 diabetes

Analysis of co-occurrence in twins and families suggests that the heritability of type 2 diabetes, i.e. the proportion of type 2 diabetes cases attributable to genetic variation, ranges between 25% and 72% [2, 3]. Several genome-wide association studies (GWAS) have been carried out to identify genetic risk variants for type 2 diabetes, which have uncovered a highly polygenic architecture of the disease [7, 8]. To date, more than 500 genetic loci have been identified for association with increased risk of type 2 diabetes, many of which show heterogeneity in allele frequencies and effect sizes across genetic ancestries [8, 9]. The effect sizes of the loci range from a 1.03-fold increase in type 2 diabetes risk for variants that are common in the population (minor allele frequency >1%) up to an eightfold increase for rare variants. For the vast majority of the loci, it remains unclear whether the identified variants are the causal variants or just in linkage disequilibrium with the causal variants [7]. Altogether, genome-wide chip data explain <20% of type 2 diabetes risk (i.e. 25–70% of the general heritability of type 2 diabetes). The 'missing heritability' is likely to be primarily due to unidentified loci with additive genetic effects [10], but could also, in part, be explained by recessive genetic effects, gene–gene interactions and gene–environment interactions [7, 8].

The majority of the identified loci are implicated in pancreatic beta cell dysfunction, with fewer loci being linked to obesity or insulin resistance [7]. Follow-up studies of the identified loci have revealed more specific mechanistic subgroups. Of the loci associated with lower beta cell function, some increase proinsulin levels, whereas others show the opposite effect, indicating different roles in insulin production [11]. Among the loci associated with insulin resistance, many result in a lipodystrophy-like profile of lower and poorly functioning overall body fat, but higher insulin resistance. Combining the genetic loci linked to specific mechanistic clusters may allow us to construct partitioned polygenic scores that identify individuals with a high genetic predisposition for certain disease mechanisms, possibly reflecting different aetiological subtypes of type 2 diabetes [11]. This mechanistic heterogeneity may contribute to different subtypes of type 2 diabetes with different clinical manifestations and prognoses [4–6].

Environmental risk factors of type 2 diabetes

Environmental influences differ between individuals in terms of which environmental factors they are exposed to, how much of these factors they are exposed to and how strong the effects are on risk of type 2 diabetes. It is important to distinguish between the general environment, which is, in principle, common to all members of a population segment at interest, and the individual environment (Fig. 1). Examples of components of the general environment are easy access to energy-dense foods and drinks, and to devices that make physical activity superfluous. The individual environment consists of individual behaviours relating to the use of these offers, which may differ between individuals because of diversity of the general environment or because the behaviours are being enforced, taught or nudged by others, or chosen by the individuals themselves, reflecting individual preferences. Differences in behaviours are partly determined by genetic differences [12–14], which may also interact with a particular environment.

The rapid and massive worldwide increase in type 2 diabetes incidence over the previous decades indicates that environmental factors have had a substantial influence [15]. The rise has occurred in parallel with an ecological transition involving rapid changes in living circumstances, such as economic development, urbanisation and increased ageing of populations [15]. The two changes that are considered particularly important in relation to the rise in type 2 diabetes incidence are increased access to energy-dense, palatable and cheap food and sugary beverages, and the reduced demand for physical activity in daily life that allows more time to be spent sedentary. Despite the overall economic improvement, poor socioeconomic circumstances within each society remain a major risk factor of type 2 diabetes, clustering together with many other risk factors. Overall, this general environment is also encompassing the so-called 'obesogenic' environment, which leads to the concept of the 'diabesity' epidemic, referring to the dual epidemic of obesity and type 2 diabetes [15]. However, it is also clear that there is not a one-to-one relation between the rise in obesity and incidence of type 2 diabetes. For example, type 2 diabetes incidence relative to obesity is much greater in Asian than in Western populations [8, 9], which may reflect both environmental and genetic differences.

Several trials enrolling individuals with impaired glucose tolerance have shown that it is possible to delay or prevent the development of type 2 diabetes by modification of individual eating and exercise behaviours [16]. The effects appear to be partially mediated by an accompanying moderate weight loss. Alterations of the gut microbiota may also be involved as mediators of the effects of the diet [17–19]. However, there is wide heterogeneity between individuals in the ability to adopt and maintain the beneficial behavioural alterations, as well as in the response to the same intensity of behavioural alteration, resulting in a wide range of outcomes. Identifying genetic and other factors important for these individual differences, and ways to manage their influence, is of major interest and could ultimately help to improve prevention of type 2 diabetes and its associated comorbidities.

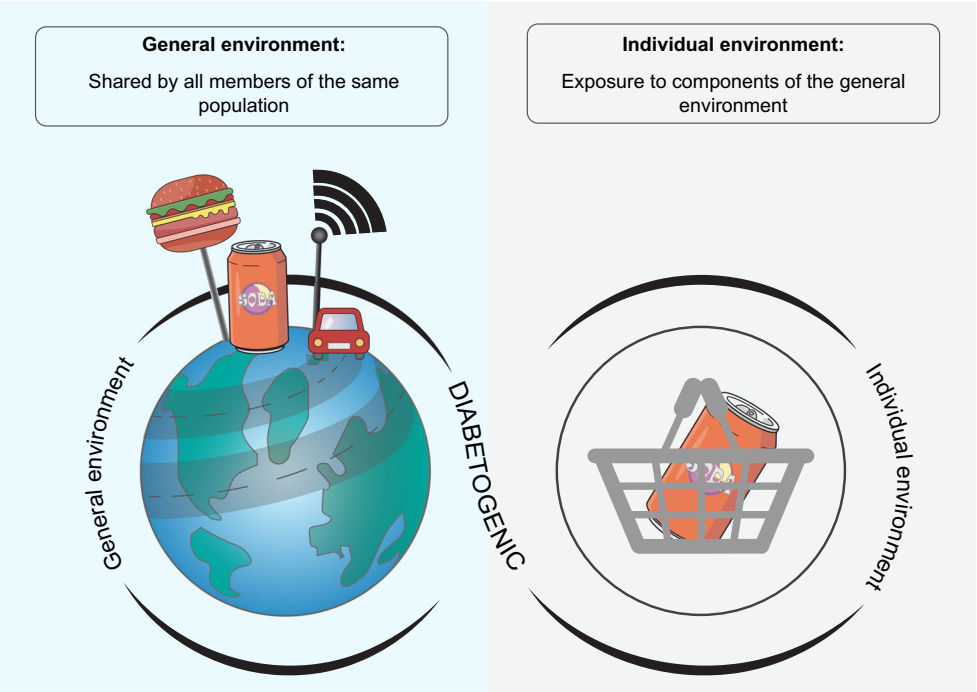

Fig. 1 The diabetogenic environment may be divided into the general environment and the individual environment. The general diabetogenic environment describes, for example, the excess availability of palatable foods and drinks, which increases energy intake, and the access to technologies and infrastructure that decrease the need for physical activity. The general environment may differ between populations, but is essentially shared by all individuals in the same population. On the other hand, the individual environment varies between individuals within the same population as it is affected, for example, by socioeconomic factors and personal choice. This figure is available as part of a downloadable slideset

What is a gene–environment interaction?

A gene–environment interaction takes place when the disease risk associated with an environmental factor differs between the genotypes of a genetic variant or the values of a polygenic score (Fig. 2). The interaction implies that the risk is either greater or lower (synergistic or antagonistic interaction, respectively) than expected from the combined effect of the environmental and genetic factors. A synergistic interaction may be illustrated by the most extreme example, where the disease occurs only if the individual carries one particular genetic variant and is also exposed to one particular specific environmental factor. This was first and clearly demonstrated in Følling's disease (phenylketonuria), a monogenic disease where a mutation in the *PAH* gene (encoding phenylalanine hydroxylase) leads to a build-up of dietary phenylalanine to toxic levels unless the individual limits intake of foods containing phenylalanine [20]. While no similar, clear-cut interaction effect has been observed in the pathogenesis of diabetes, it is well-established that different forms of monogenic diabetes (MODY) show variable responses to therapies depending on the underlying pathological mutation [21], underlining a role for gene–treatment interaction in the management of glucose homeostasis.

Gene–environment interactions in the development of type 2 diabetes are likely to be very subtle, requiring very large sample sizes and accurate and precise measurement of the underlying environmental and behavioural exposures for their identification [22, 23]. Sometimes the statistical power to identify a gene–environment interaction may be enhanced by combining multiple genetic and environmental influences into scores. However, the limitation of this approach is that not all variants may interact with the same environmental exposures; thus, the interaction effects between individual variants and specific environmental exposures may be hidden when analysed in combination with other variants and exposures, possibly creating effects in the opposite direction. This is one major challenge in deciphering gene–environment interactions in type 2 diabetes and other diseases in which multiple genes and environmental factors determine risk [24].

Evidence of gene–environment interactions in obesity

Evidence from a range of studies suggest that a synergistic interaction between genes and the environment may underlie the development of obesity and, consequently, type 2 diabetes. The populations that have seen most dramatic rise in the

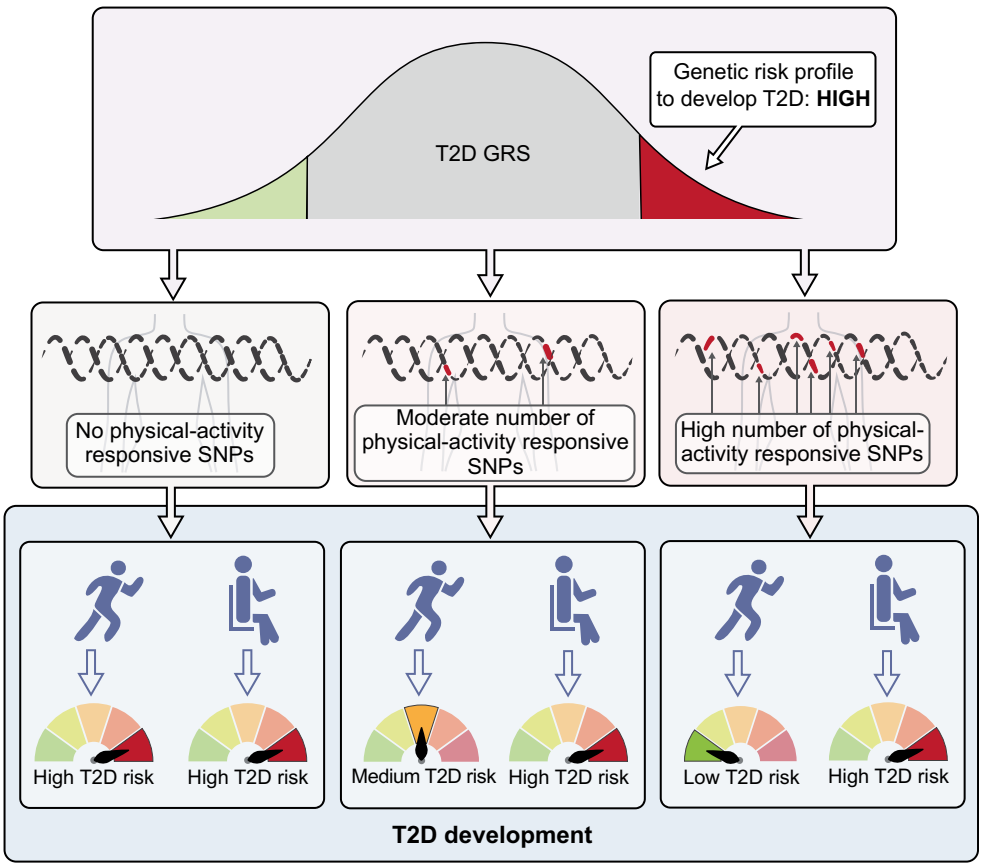

Fig. 2 Hypothetical example of a gene–environment interaction in the development of type 2 diabetes (T2D). The genetic risk profile for T2D can interact with environmental factors, such as physical activity. A gene–physical activity interaction could, for example, imply that individuals with a high genetic risk of T2D have different risk reductions with physical activity, depending on the number of physical-activity responsive risk variants they carry. This could support precision prevention of T2D with physical activity, based on genetic profiling. GRS, genetic risk score. This figure is available as part of a downloadable slideset

prevalence of obesity and type 2 diabetes are certain indigenous populations, such as Polynesian, Aboriginal Australian and Native American individuals. Among the Pima Indian population living in Arizona (USA), the prevalence of obesity and type 2 diabetes was low until the 1950s; however, exposure to the Western living environment triggered a rapid increase in the prevalence of these conditions. By the early 2000s, the prevalence of type 2 diabetes in Pima Indian individuals in Arizona had reached the highest recorded, with more than 50% of adults above the age of 35 years being affected in this population [25]. Segregation analyses have shown strong familial aggregation of type 2 diabetes in Pima Indian families, suggesting a genetic basis for the disease [26]. Among a distinct population of Pima Indian people living in Northern Mexico, who are genetically similar to the Pima Indian individuals in Arizona but have retained a traditional lifestyle, the prevalence of obesity and type 2 diabetes has continued to be low [27]. These observations could be explained by a strong genetic predisposition to obesity and type 2 diabetes among Pima Indian population that makes them exceptionally susceptible to the Western environment. However, unequivocal evidence to support such hypothesis about gene–environment interaction is lacking.

Analyses of birth cohorts have shown a more pronounced influence of genetic predisposition to obesity in individuals born in the mid 1950s, who became exposed to the obesogenic environment at a young age, as compared with individuals born earlier in the century, who were exposed in later life [28]. Studies in twins have shown higher heritability of obesity in young children who live in home environments defined as obesogenic than in children living in non-obesogenic environments [29]. The heritability of BMI status has also been found to be lower in twins who are physically active than in non-physically active twins [30, 31].

Recent analysis of UK Biobank data elucidated the population variance in BMI that may be explained by gene–environment interactions. Of eight studied self-reported factors describing diet, physical activity, smoking, alcohol consumption, social deprivation or self-reported health, only the genetic interaction effects with smoking behaviour explained a noticeable proportion of BMI variance (4.0%) [32]. The sum of variance explained by the eight behavioural or environmental covariates was 7.5%. Cross-sectional studies testing the statistical significance of the interaction of polygenic risk scores for BMI have examined interactions with a wide range of behavioural and environmental factors, of which the strongest evidence has been seen with physical activity, sedentary time, frequency of alcohol intake and social deprivation [33–35]. The findings for the strongest individual locus associated with obesity, the *FTO* locus, have been largely consistent with the findings for polygenic scores of obesity. For *FTO*, the currently strongest evidence is of interaction with physical activity and sedentary behaviour [36–40].

Overall, these results imply that gene–environment interactions play a role in today's high prevalence of obesity, but the evidence that there is a limited variance in BMI attributable to interactions suggests that this role may be modest. The analyses of interactions between polygenic scores and various environmental factors have detected several environmental factors that may modify the influence of genetic predisposition. However, the analyses have also indicated that gene–environment interaction effects may be sensitive to confounding, making it challenging to distinguish between these effects and correlated environmental exposures [35]. It is also possible that the interpretations of findings are challenged by indications of bidirectional effects, i.e. obesity may influence the behaviours [12].

Role of gene–environment interactions in type 2 diabetes development remains unclear

In contrast to BMI polygenic scores and obesity, observational studies of the interaction between type 2 diabetes polygenic scores and behavioural risk factors have not provided consistent evidence [41–45]. Observational studies have also not shown consistent evidence for an interaction of the strongest individual locus associated with type 2 diabetes, the *TCF7L2* locus, with behavioural risk factors [41, 45].

As type 2 diabetes is aetiologically complex, it is possible that the application of polygenic risk scores without consideration of the specific biological mechanisms affected by the causal genetic variants and environmental exposures may mask interaction effects. A recent analysis partitioned an overall polygenic score for type 2 diabetes into 12 component subscores according to the variants' phenotypic associations, to distinguish between disease-related pathways [46]. A significant interaction was found with physical activity for two of the component scores. This was not observed for the overall type 2 diabetes polygenic score, suggesting that the use of mechanism-specific polygenic scores may help in the discovery of gene–environment interactions.

Another possibility is that the genetic variants that have an impact on type 2 diabetes risk upon interacting with behavioural factors may differ from the variants known to predispose individuals to the development of type 2 diabetes irrespective of interaction with behavioural factors. In this scenario, large genome-wide screens specifically designed to identify interactions would be required to identify the significant variants. A recent analysis of ~340,000 individuals identified five variant–dietary trait pairs that reached genome-wide significance for interaction on the levels of HbA_{1c}, a measure of long-term blood glucose levels [47]. Four of the five loci did not show a genetic main effect and could not have been identified in a main effect GWAS for HbA_{1c}. However, an

independent replication and assessment of the causal role of the loci is warranted.

Overall, the role of gene–environment interactions in the development of type 2 diabetes remains unclear. More research is needed to study interactions between mechanism-specific polygenic scores and environmental factors relevant for the same mechanisms, and to investigate whether genetic variants interacting with environmental factors can be robustly identified through large genome-wide screens. This research will undoubtedly benefit from stratifying type 2 diabetes according to the recognised subtypes, which could be based on different sets of gene–environment interactions before the disease emerges.

Gene–environment interactions for weight loss and type 2 diabetes prevention

Twin and family studies suggest that genetic make-up may modify inter-individual differences in the responses of body weight and body composition to behavioural interventions, suggesting more similar responses in genetically related than unrelated individuals [48–51].

Despite strong observational evidence of the interaction of the *FTO* locus with the obesogenic environment, analyses of data from eight randomised clinical trials on weight loss by physical activity-, dietary- or drug-based interventions, showed no influence of the *FTO* genotype on the amount of weight loss in response to the interventions [52]. Thus, findings of interactions in observational studies may not directly translate to the context of the interventions, or the findings may imply that such interactions are more specific to certain types of interventions.

Randomised trials in the USA and Finland have investigated whether the influences of behavioural interventions (focussing on the impact of weight loss, diet and physical activity) on progression from impaired glucose tolerance to type 2 diabetes may be modified by genetic predisposition to type 2 diabetes. Both trials found that the *TCF7L2* locus was associated with a higher risk of progressing to type 2 diabetes in the control group, but not in the intervention group, suggesting that the intervention suppresses the genetic effect of the *TCF7L2* locus, although the genotype–group interaction did not reach significance [53, 54]. In the Finnish trial, family history of diabetes or polygenic risk score of type 2 diabetes did not modify the effect of the lifestyle intervention on type 2 diabetes risk [55]. The US trial also showed no significant interaction between a polygenic risk score of type 2 diabetes based on 34 variants and the behavioural intervention, although the incidence of type 2 diabetes was significantly higher in the top quartile of the polygenic risk score in the intervention group than in the control group [56]. An expanded score of 67 variants showed a significant multiplicative interaction with reaching the diet goal of the intervention (total fat intake <25% of total energy) on reducing type 2 diabetes incidence, but not with the weight loss or physical activity goals [57]. The US trial showed no significant interaction between a polygenic risk score for a lipodystrophy-like phenotype and lifestyle intervention on type 2 diabetes incidence [58]. In addition, no significant interaction was seen between a polygenic risk score for coronary artery disease and the lifestyle intervention or its components on diabetes-incidence or cardiometabolic risk factors after correction for multiple testing [59].

Overall, the current evidence suggests that behavioural interventions are effective in reducing body weight and risk of type 2 diabetes, regardless of underlying genetic predisposition, but there may be some differences in the effects that are dependent on underlying genetic risk.

Future translational aspects

The ultimate implementation goal of unravelling gene–environment interactions in the development of type 2 diabetes and its precursor conditions, such as glucose intolerance and being overweight, is to improve opportunities for type 2 diabetes prevention. Knowing which particular genetic profile each individual has with regard to predisposition to type 2 diabetes could allow sorting individuals by the level of genetically determined risk of type 2 diabetes and setting a threshold of risk level above which it is justified to intervene to reduce the risk. Among the individuals above this risk level, the particular composition of the genetic profile, constituting the elevated risk, would be expected to call for tailored prevention, in which the environmental exposure presumed to interact with the genetic profile is targeted to reduce the risk of type 2 diabetes.

When comparing this to strategies for prevention where information of such genetic profiles is not available, the addition of the genetic information may leverage the prevention to so-called precision prevention [60]. This means that the prevention is more precisely tailored to individual needs than what the currently applied strategies not considering genetic information would allow. This increased precision would be expected to provide a better outcome for the whole group, both by targeting the effective intervention to the individuals in need and avoiding interventions in individuals for whom the particular intervention does not work or may produce serious adverse effects, or for whom there may be no reason to intervene because the risk is so low. This strategy could benefit from the identification of aetiologically different subtypes of type 2 diabetes. If there are clearly defined genetic differences that together with particular environmental factors or behaviours associate with the subtypes, then the differences in prognoses of the subtypes could help to prioritise efforts to prevent specific forms of type 2 diabetes with a poor prognosis.

Whilst this is the vision of future prevention of type 2 diabetes, it is clear from the above review that the currently available evidence of interactions between genes and the environment is so limited that there is not yet a basis for utilising the information in the fight against type 2 diabetes in this way. The current state-of-the-art in the understanding of the role of gene–environment interaction in type 2 diabetes risk is not mature enough for attempts to translate into proposed actions.

In the hope that such evidence may emerge in the foreseeable future, a major challenge of the next stage in the process will be to prove, using randomised trials, that providing such tailored intervention produces an overall improved outcome. The more the profiles for type 2 diabetes risk become individualised, the smaller the groups become for the comparison of alternative interventions in trials. It is likely that such trials will only be feasible on the basis of large-scale consortia that assemble large enough study populations for recruitment, in order to achieve sample sizes that allow for the production of statistically valid results within defined subgroups. By such broadening of the trial basis, it is likely that the heterogeneity of the study populations will increase, which will further enhance the need for even larger study populations.

Assuming that the interventions would encompass modifications of behaviours in the realm of the common 'lifestyle' that are pertinent as risk factors not only for type 2 diabetes but also for many other ailments, it may be questionable to tailor the actions according to specific beneficial effects on type 2 diabetes risk only. Withholding the intervention from people at low risk of type 2 diabetes would ignore the possibly elevated risk of other diseases. Moreover, according to the current knowledge, the modifications of the behaviours should be sustained over long time periods, which remains a major challenge. This raises doubt as to whether knowing about one's own genetic profile will help the individual to stay on the new behavioural track more consistently and for a longer time [61].

Given the high and ever-increasing global incidence of type 2 diabetes, with its strong inverse social gradient, an individualised approach, which is very demanding for the primary care health services and for the individuals themselves, could be destined to fail in reducing type 2 diabetes incidence. The ideal prevention is likely to be achieved by an alteration of factors of the general environment that are responsible for the global rise in incidence of the disease back to previous levels. The mere fact that the incidence of type 2 diabetes has risen, and done so in a very heterogeneous way between population segments across the world, implies that, in principle, it should be possible to find ways to reverse it.

The assumed core components of the diabesity epidemic include those that lead to reduced physical activity, both during work and leisure time, resulting in increased sedentary behaviour, and the excess consumption of cheap, energy-dense and tasty food and sugary beverages. These factors are integral parts of societal changes that, alone, are broadly conceived to provide multiple apparent benefits, such as less poverty and more comfortable lives, not least for the more socially deprived population segments. The pivotal dilemma becomes obvious when comparing the globally increasing life expectancy that is induced by improved social environments with the age-dependent steep rise in the incidence of type 2 diabetes. It, therefore, becomes a major cultural and political obstacle to use so-called societal structural interventions to alter the general environment by regulating the availability of its diabetogenic components. Dedicated attempts have been made in various societies but, so far, without achieving the desired decline in diabetes incidence [62–64]. The hope lies in a global, societal and cultural transition that will make our living environment less diabetogenic.

Conclusions

There is no doubt that individual genetic profiles and the environment and behaviours, especially those related to obesity, physical activity and diet, have a major role in development of type 2 diabetes. The rapid global rise in the incidence of type 2 diabetes, in parallel with obesity, must be driven by changes in the common environment, which are deeply embedded in the concurrent societal changes. The opportunities for reversal of the epidemic of type 2 diabetes may, therefore, depend on a profound transformation of the global environment to become less diabetogenic.

There are obvious gaps in our understanding of the role of gene–environment interactions in the development of type 2 diabetes and its putative subtypes. Continued efforts to unravel gene–environment interactions are important to increase our understanding of the aetiology of type 2 diabetes and its subtypes. The currently available evidence does not support translation of this evidence to individualised preventive actions, and generating more supportive evidence in the settings of public health is likely to require major international efforts. It is important to recognise that the use of new information for the prevention of type 2 diabetes and its subtypes would require that the particular combinations of genetic and interacting environmental or behavioural factors are identifiable before the emergence of the disease, and that targeted preventive interventions have been shown to reduce the risk of later development of the disease.

Supplementary Information The online version contains a slideset of the figures for download, which is available to authorised users at https://doi.org/10.1007/s00125-021-05639-5.

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