Environmental risk factors of type 2 diabetes – an exposome approach

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Tweet (250 characters): Air pollution, residential noise and area-level socioeconomic deprivation increase risk of type diabetes, while neighbourhood walkability and green space reduce risk of type 2 diabetes.

Abstract

Type 2 diabetes is one of the major chronic diseases accounting for a substantial proportion of disease burden in Western countries. The majority of the burden of type 2 diabetes is attributed to environmental risks and modifiable risk factors such as lifestyle. The environment we live in and changes thereof can thus contribute substantially to the prevention of type 2 diabetes at a population level. The "exposome" represents the (measurable) totality of environmental, i.e., nongenetic, drivers of health and disease. The external exposome comprises aspects of the built environment; the social environment; the physico-chemical environment and the lifestyle/food environment. The internal exposome comprises measurements at the epigenetic, transcript, proteome, microbiome, or metabolome level to study either the exposures directly, the imprints these exposures leave in the biological system, the potential of the body to combat environmental insults and/or the biology itself. In this review, we aim to describe the evidence on environmental risk factors of type 2 diabetes focusing on both the general external exposome and imprints thereof on the internal exposome. Studies provided consistent evidence that air pollution, residential noise and area-level socioeconomic deprivation are associated with an increased risk or type 2 diabetes, while neighbourhood walkability, green space are associated with a reduced risk of type 2 diabetes. There is little or inconsistent evidence on the contribution of the food environment, other aspects of the social environment and outdoor temperature. These environmental factors are thought to affect risk of type 2 diabetes mainly through mechanisms incorporating lifestyle factors such as physical activity or diet, the microbiome, inflammation or chronic stress. To further assess causality of these associations, future studies should focus on investigating the longitudinal effects of (changes in) our environment in relation to risk of type 2 diabetes and whether these associations are explained by these proposed mechanisms.

Introduction

Type 2 diabetes is a major chronic disease burden in Western countries, estimated to affect 642 million people worldwide by 2040 (1). Its increasing prevalence can be explained by non-modifiable factors, such as the ageing of the population and modifiable factors like the overweight/obesity pandemic and unhealthy lifestyle habits (1, 2). Large prevention trials indeed show an approximately 50% reduced risk of type 2 diabetes with lifestyle modification in high-risk populations (3). However, translation of such interventions into real-life and less-controlled settings is challenging (4) with an overall risk reduction of 15% remaining after 6 years (5). One reason for this reduced effectiveness is that the overwhelming majority of the interventions rely on cognitive capacities and intrinsic motivation of those targeted (6). More impact may be expected if the environment is explicitly accounted for in interventions.

The human genome project revolutionized our understanding of the genetic origins of disease. Genome-wide association studies estimate that genetic variation solely explains 15-20% of the burden of type 2 diabetes (7), although other studies show a genetic contribution estimated around 45%, albeit with a wide range (8). Nevertheless, a large part of the burden of type 2 diabetes is attributed to modifiable and/or environmental risk factors and its interactions with our genetic make-up. Indeed, studies have reported population attributable fractions of 48% for obesity, 40% for a diet low in whole grains, 30% for physical inactivity and 10% for smoking (9). However, a large part of the environmental drivers of type 2 diabetes remain unknown hampering the development of effective prevention programs. One reason for the lack of understanding of the environmental drivers of type 2 diabetes is the lack of good measures of our ‘environment’ both in coverage (the number of environmental factors that can be quantified) and resolution (the quality with which the proxies capture true exposure).

To address the imbalance of our abilities to measure environmental factors as compared to genetic factors the term ‘exposome’ was coined in 2005 (10). The ‘exposome’ represents the (measurable) totality of environmental, i.e., nongenetic, drivers of health and disease (10). Thus, analyses of biological perturbations at different molecular levels, together with environmental measurements, should provide insights on the internal and external exposome contributors (11).

The external contributors to the exposome (i.e. general external exposome) comprises aspects of the built environment (characteristics of the physical space where we live, work); the social environment (with whom we interact or our socioeconomic position); the physico-chemical environment (chemical substances or physical agents we are exposed to) and the lifestyle/food environment (what we eat or how much we exercise) (Figure 1) (11). The specific external exposome refers to individual exposures such as health behaviours or medication use. The internal exposome includes measurements at the epigenetic, transcriptome, proteome, microbiome, or metabolome level to study either the exposures directly (e.g. non-targeted chemical screening (12)), the exposure imprints (e.g. biological imprints of smoking in the epigenome (13)), the potential of the body to combat environmental insults (i.e. allostatic load (14)), and/or the biology itself (Figure 1) (15).

In this review, we describe the evidence on environmental risk factors of type 2 diabetes focusing on both the general external exposome and imprints thereof on the internal exposome. Because individual-level aspects of the specific external exposome such as dietary patterns, physical activity and lifestyle modification programs have been reviewed elsewhere (3, 16), these factors will not be included. We provided a relative grading of the evidence indicated as stronger versus weaker evidence on a specific relation. A stronger grading is provided when a systematic review or meta-analysis reported consistent results in at least three studies, and a weaker grading was provided when only incidental studies reported on the specific relation. We evaluated the evidence intermediate when a systematic review or meta-analysis with at least three studies did not yield consistent evidence. We conclude by providing methodological considerations and future perspectives for exposome research in the field of type 2 diabetes.

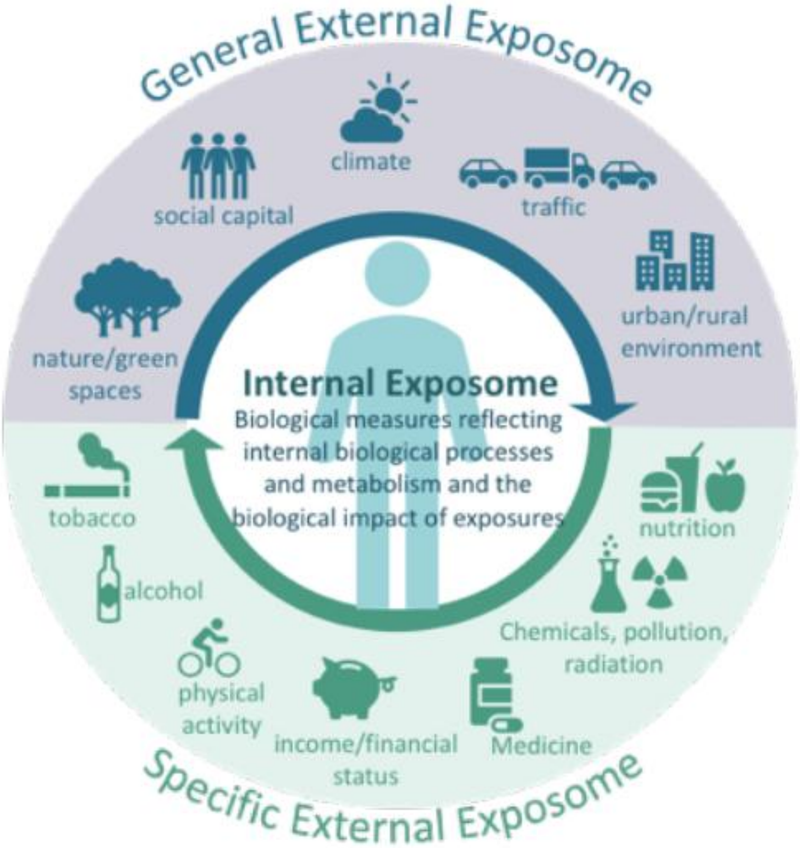

Figure 1: The three different domains from the exposome as adapted from Wild et al. 2005.

Environmental risk factors of type 2 diabetes

The food environment

The food environment encompasses the accessibility, availability, affordability and promotion of foods and food retailers (17). The investigation of the food environment in relation to diet quality, obesity, and chronic disease risk gained interest due to evidence of 'food deserts' in North America. Living in a 'food desert' with virtually no geographical access to food retailers has been associated with lower diet quality or disease outcomes (18). Similarly, 'food swamps' represent environments where unhealthy food options outweigh healthy options.

Studies investigating exposure to the food environment in relation to diet quality or type 2 diabetes most frequently define the food environment as geographic availability and accessibility to food retailers in the home neighbourhood, mainly operationalized as measures derived from underlying spatial data of density of or distance to a specific food outlet (19-21). Exposure to unhealthy food retailers such as takeaway and fast food outlets has indeed been associated with less healthy diets, obesity, increased insulin resistance, increased triglycerides concentration, and type 2 diabetes in some studies mainly performed in the United States (22-24). Despite these promising findings for a link between the food environment and type 2 diabetes, recent systematic reviews including over 15 studies report inconsistent findings or null results (Figure 2) (20, 25, 26). Subjective measures of exposure to food retailers such as perceived availability or use of food retailers are more consistently associated with type 2 diabetes risk than objective measures (27, 28). Finally, interventions on changes in the exposure to food retailers are scarce, but a natural experiment on residential relocation after the 2011 Japan Earthquake and Tsunami suggested that shortened distances to food outlets increased the risk of obesity and other cardiometabolic risk factors (29, 30).

The main reasons explaining these inconsistencies are: the over-simplistic definition of 'exposure', ignoring other environmental attributes like the social environment; the focus on the residential neighbourhood only and not accounting for exposure to the food environment at work or in transit; and lack of insight into individuals' behavioural interactions with the food environment (19-21, 26, 31, 32). Changes in the spatial distribution of food outlets over time might also play a role, as several studies showed substantial changes in the food environment mostly with increases of unhealthier food outlets particularly in neighbourhoods with low socioeconomic position (33-36). Whether such changes also affect the observed associations of the food environment with risk of type 2 diabetes has been scarcely investigated. A study from Mexico prospectively analyzed changes in the food environment in relation to diabetes found that individuals living in neighborhoods that experienced a decrease in the density of fruit and vegetables stores, and an increase in the density of convenience stores had higher odds of diabetes as compared to individuals living in neighborhoods where these stores did not change (37).

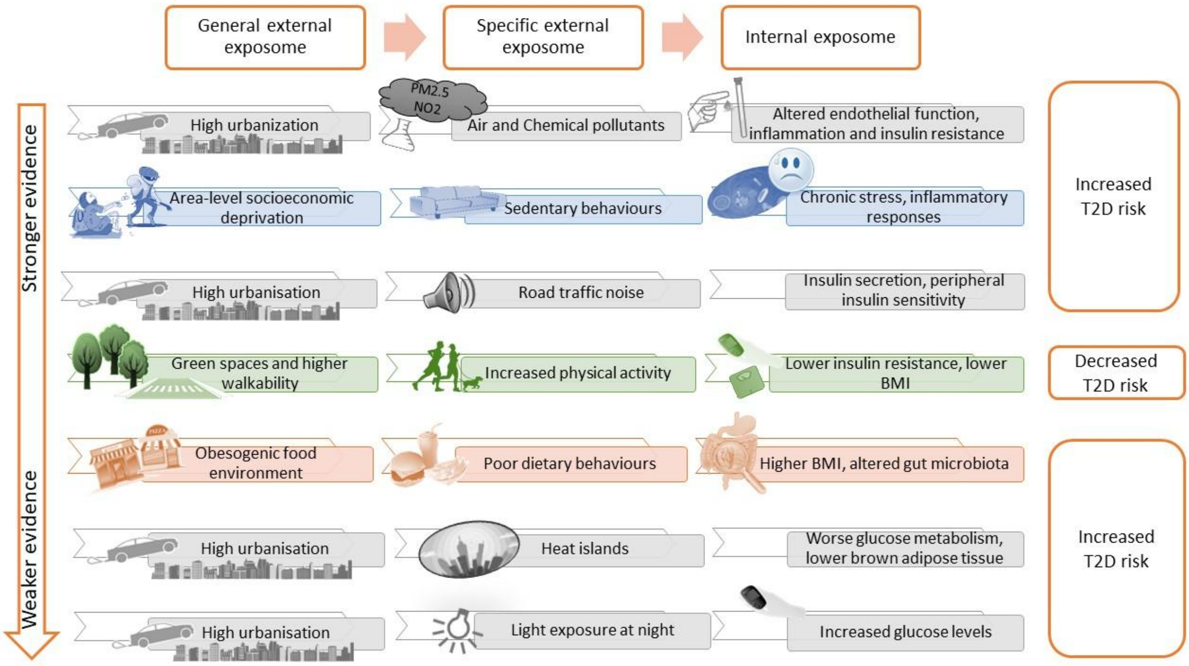

Figure 2. Overview of the evidence and potential pathways of different aspects of the external exposome in relation to risk of type 2 diabetes.

The built environment

The built environment is defined as man-made characteristics of the physical environment in which people live, work and recreate, including buildings, streets, open spaces, and infrastructure (38, 39). The built environment is hypothesized to be associated with type 2 diabetes incidence primarily through physical activity related pathways (40). Indeed, meta-analyses of 6 and 4 studies respectively consistently show that living in neighbourhoods with high walkability and green space is associated with a 10-20% lower risk of type 2 diabetes (20, 25, 26), although the majority of evidence stems from North-American and Australian studies, while evidence for European countries is limited (Figure 2). Walkability of a neighbourhood is characterized by population density, land-use mix (heterogeneity of land uses in an area such as residential, industrial and natural), and connectivity (i.e. intersections). Some studies furthermore showed that physical activity indeed partly explained the association between walkability and risk of type 2 diabetes (41). Other elements of the built environment in relation to risk of type 2 diabetes have not been investigated intensively. Six studies investigated availability of sports facilities in relation to risk of type 2 diabetes, but reported inconsistent results ranging from no association to a reduced risk with a higher availability (26). A systematic review showed that environmental interventions to increase physical activity by changes in the built environment generally improved levels of physical activity (42), but effects on type 2 diabetes have not been evaluated. Furthermore, a large Finnish cohort study of over 100.000 individuals showed that changes in residential greenness were associated with a 12% reduced risk of type 2 diabetes (43). Finally, a range of over 40 studies show that urban dwellers of particularly low and middle income countries have a 40% increased risk of type 2 diabetes (26), but the underlying drivers of this association are not entirely clear. Apart from mainly physical activity related pathways, the built environment is characterized by interrelated factors (26, 44) that not only influence human behaviour, but can also directly affect a range of health-relevant environmental exposures such as noise or air pollution. These exposures have been investigated as part of the physico-chemical environment.

Physico-chemical environment

Air pollution has been documented to change endothelial function, trigger inflammation and insulin resistance, and is associated with elevated risk of hypertension (20). Recent findings also suggest that it can alter the gut microbiota (45). Recent meta-analyses including up to 86 studies showed an increased risk of type 2 diabetes with increased exposure to air pollution, with odds ratios (per 10 µg/m3 increase) ranging from 1.08 – 1.10 for particulate matter smaller than 2.5 micron (PM2.5); 1.10- 1.12 for PM smaller than 10 (PM10) micron and 1.05- 1.08 for nitrogen dioxide (NO2) (Figure 2) (20, 46). Studies also suggested women to be more susceptible from exposure to pollution, because they spend more time in and around the home than men (20). Data on other pollutants are very limited, although a recent study showed Sulphur dioxide as a risk factor (47). There is inconsistency as to what pollutant is mostly correlated to type 2 diabetes, mainly because of the limited number and mixed results of multi-pollutant models (20).

Although there are only a few studies investigated the effect of light exposure and metabolic diseases (48) a relatively large study in Japanese care settings indicated that night light exposure could be associated with T2D (49). This association could be explained by potential mediating effects of lifestyle, particularly sleep disruption, that could essentially result into elevated glucose levels (50).

Two meta-analyses of 5 studies also showed consistent evidence of an increased risk of type 2 diabetes with higher residential, but not occupational, noise exposure (Figure 2) (26, 51). Noise can act as an environmental stressor that leads to insulin secretion and peripheral insulin sensitivity (51), but other lifestyle factors such as sleep may also be involved (51). Finally, the associations for noise and light could be confounded by other factors associated with urbanization such as air pollution.

Higher body temperature could negatively affect glucose metabolism as well by decreasing the brown adipose tissue mass and activity (52). Experimental studies report high efficiency of cold exposure as a potential therapy for type 2 diabetes (53, 54). Nevertheless, very few studies explored the quantitative association between ambient temperature and incidence of type 2 diabetes with the exception of one study reporting a higher diabetes incidence with increasing annual outdoor temperature (55).

Finally, several meta-analyses including seven or more studies showed that chemical pollutants, such as persistent organic pollutants (56), pesticides (57) and heavy metals (58) are consistently associated with an increased risk of type 2 diabetes. These pollutants may originate from the complex chemical environment including occupational hazard, air or water pollution, food and so on. Many results suggest a stronger association for women and individuals with overweight or obesity (58).

Social environment

The social environment is generally understood as the social relationships and social context in which groups of people live and interact. It is composed of several components and often operates at various levels of influence (59). Examples include area-level deprivation, social capital, ethnic segregation and perceived safety. While individual-level social factors (e.g. education, income) are consistently associated with type 2 diabetes risk (60, 61), environmental social factors are recently receiving increased attention.

Systematic reviews of over 10 studies consistently show that area-level socioeconomic deprivation is associated with an up to two-fold increased incidence of type 2 diabetes (Figure 2) (25, 62, 63). In line with these studies and suggesting causal relationship, natural experiments and studies of residential relocation show that moving to low deprivation neighbourhoods reduced HbA1c and risk of type 2 diabetes (43, 64, 65). Despite growing evidence on the relation of social capital with health (66), the few studies investigating social capital and type 2 diabetes incidence present mixed findings (62, 66-69). Concerning social networks, even though its importance as a risk factor for type 2 diabetes has been shown in large longitudinal studies, experimental studies are lacking (70). Less is known on the impact of ethnic segregation on type 2 diabetes incidence. Nonetheless, a review of Kershaw & Pender (2016) concluded that ethnic segregation can influence the severity of type 2 diabetes but not its development (71). Regarding discrimination, studies mostly investigated the impact of individually experienced but not neighbourhood level discrimination on type 2 diabetes incidence (72). Furthermore, only few studies investigated the impact of perceived crime within the neighbourhood on type 2 diabetes incidence, with some finding a significant association (73), and others indicating that it has a weak moderating role between the local density of amenities and type 2 diabetes incidence (74).

Social environment factors are hypothesised to influence type 2 diabetes incidence through lifestyle behaviours (*e.g.,* sedentary behaviour) (75-78) and/or chronic stress and inflammatory responses (79, 80). Even though the evidence on the association between certain components of the social environment and risk of type 2 diabetes may be sparse or inconclusive, stronger links have been observed between social environment factors and lifestyle behaviours and obesity (71, 81), suggesting a plausible link with type 2 diabetes.

Internal Exposome

Although our internal exposome consists of proteins, lipids, metabolites and so on, the role of the metabolome and microbiome appear to be of particular importance in the etiology of type 2 diabetes.

The microbiome

The gut microbiota is known for its ability to modulate inflammation, metabolize xenobiotics, maintain intestinal integrity and its interactions with dietary components. Changes in the abundance and diversity of the gut microbiota have been linked to the progression of many metabolic diseases, including type 2 diabetes (82-84). The specific associations between the gut microbiome and type 2 diabetes in humans have conveyed conflicting results, which at least partly can be explained by large methodological differences in microbiome studies (82-84). Nevertheless, an analysis of over 40 observational studies has identified specific members of the gut microbiome that appear to be consistently associated with type 2 diabetes (82). Five genera showed a recurrent protective role in relation to type 2 diabetes (*Bacteroides*, *Bifidobacterium*, *Akkermansia*, *Roseburia* and *Faecalibacterium).* These genera are associated with several metabolic mechanisms that affect host physiology, such as reduction of endotoxemia, increase of energy yield, drug metabolism, decrease of tissue inflammation and production of bacterial metabolites (82, 83, 85-87). Gou *et al.* recently applied a machine learning framework to correlate gut microbiome features to type 2 diabetes in large scale cohorts (88). The authors report 14 microbial features to predict type 2 diabetes risk, which were used to construct a microbial risk score (MRS) and further correlated to microbiota-derived blood metabolites and other lifestyle factors. The same study demonstrated that the MRS yielded a superior disease prediction accuracy than other environmental aspects (i.e. lifestyle, diet and host genetics). The combination of all factors, however, showed the highest predictive accuracy (88). This and other association studies highlight the role of the microbiome in type 2 diabetes, but the complex interaction of gut microbiome with environmental factors, and their link to the onset and progression of type 2 diabetes requires further research.

Metabolome and exposome scans

Technological developments, in which untargeted liquid- (LC-) and gas (GC-) chromatography are combined with high-resolution mass spectrometry (HRMS), have made it possible to comprehensively and in a high-throughput fashion measure the patterns of (1000s of) metabolites that are present in biological fluids, known as the metabolome (89, 90). The metabolome provides a picture of the functional status of the biological system and as such can provide insights into the pathophysiology of type 2 diabetes and enables identification of type 2 diabetes biomarkers (89, 90). A number of endogenous metabolites were identified as early biomarkers of type 2 diabetes, including branched-chain amino acids, aromatic amino acids, 2-aminoadipic acid, sphingomyelin, glycine, acyl-alkyl-phosphatidylcholines, lysophosphatidylcholine, hexose, -hydroxybutyrate, Linoleoylglycerophosphocholine, and Glyoxylate (90-95).

In light of possibilities for future (public health) interventions, it is of interest to assess which environmental factors impact type 2 diabetes directly or through perturbations of the metabolome. In a study by Patel et al. 266 environmental factors measured in urine or blood as part of the National Health and Nutrition Examination Survey were investigated (96). The pesticide derivative heptachlor epoxide, vitamin γ-tocopherol, and specific polychlorinated biphenyls were identified as risk factors for type 2 diabetes and β-carotenes (among others) were identified as protective factors for type 2 diabetes.

Recent optimisation of LC-HRMS and GC-HRMS platforms combined with innovative new data extraction approaches now enable the detection of an even wider range of exposure-related chemicals present at very low concentrations in biological fluids (e.g. blood, urine) (15). Application to human populations allows detection and characterisation of a large range of exogenously derived small chemicals including pharmaceuticals, pesticides, preservatives, dietary compounds and microbial metabolites in small quantities of biological materials (97). Collectively, these measurements provide a snapshot of the internal exposome, which can be used to elucidate some of the underlying biological mechanisms of how known or suspected risk factors such as heavy metals (98-101), other trace elements (102), persistent organic pollutants (103, 104), drug use (105) and air pollution (106) contribute to the development of type 2 diabetes.

Methodological considerations

Since our living environment mostly is an indirect determinant of type 2 diabetes, causal inference is challenging and the putative underlying mechanisms are difficult to disentangle. Because changes in the environment are often difficult to investigate in controlled studies, the majority of evidence on environmental risk factors of type 2 diabetes stems from observational studies, which might be susceptible to reverse causation, as residence preference and selection is not a random process (107). However, most studies cannot control for such processes underlying choice of residence. Moreover, environmental characteristics often correlate for a certain location. For example, urbanization is often associated with socioeconomic status of a neighbourhood and certain food outlets also cluster in highly urbanized neighbourhoods with lower socioeconomic status. Altogether, these aspects make it difficult to assess causality based on observational studies. Longitudinal studies and particularly natural experiments may offer insights into such reverse causation and confounding factors. Such studies could account for changes in the living environment in relation to incidence of type 2 diabetes either by selecting a cohort of people moving to a different location to study the changes in living environment or by selecting a cohort of people residing in the same location for a longer time period to study environmental changes in this neighbourhood in relation to type 2 diabetes. However, such studies thus far are scarce. Furthermore, for certain environmental factors, with the exception of the food environment (35), changes over time will be small and development of type 2 diabetes is slow, warranting long follow-up durations (108, 109). Natural experiments, for instance implementing a new car-free cycling zone or limiting fast-food outlets in certain regions, may offer additional evidence by creating a sudden and larger change in the environment. Most studies have focused on residential living environment, while activity space (routes, destinations, work environments) is likely of relevance, as well as individual's interaction with their environments (110). Finally, although urban residence is associated with an increased risk of type 2 diabetes compared to rural residence particularly in low- and middle-income countries (26), for other environmental risk factors evidence almost primarily comes from high-income countries (20, 25, 26). With the exception of a few studies addressing effect modification by sex, ethnicity, income or other characteristics (28, 111), little is known about differential effects of environmental factors across subpopulations based on sex or ethnicity, which should be further investigated.

A more thorough understanding of the underlying biological pathways linking the environment to risk of type 2 diabetes may also help in assessing causality. In addition to providing deeper biological insights into previously identified risk factors, assessment of the internal exposome will contribute to the identification of currently unknown risk factors of type 2 diabetes, and especially will provide insight into how these exogenous chemicals collectively interact with type 2 diabetes risk profiles (11). Such insights require the application of advanced methods for annotation (97), and statistical and biological interpretation of the generated data (11). Large studies are needed to make solid inferences using complex and high-dimensional data.

Even though high quality methods are available today, a lot of progress can still be made in terms of the quality of the assessment of the living environment. This pertains to both the external and the internal exposome. The type of tools and methods that are needed varies from domain to domain, but should typically incorporate the ability to assess a wide range of factors with high sensitivity. Several recent reviews provided a critical overview of the tools and methods that are currently available for exposome studies and indicates where progress can still be made (15).

Future perspectives

Future studies should investigate longitudinal changes in our environment in relation to risk of type 2 diabetes, including pathway analyses of health behaviours. Effects on the microbiome or endogenous metabolites should also be incorporated, to investigate underlying pathways of the association with type 2 diabetes through effects on health behaviours, stress responses or inflammation. By analysing not only the gut microbiome in relation to the disease, but also considering the influence of other environmental exposures, such as diet, pollution and medications, as well as host metabolism, we expect to be able to better understand the role of the gut microbiome in type 2 diabetes. For example for light at night, more research is necessary to understand the underlying mechanism in the association with risk of type 2 diabetes, as it is suggested that hormonal levels, circadian rhythms or sleep quality, may play a role in these associations (49).

For the food environment, exposure should be operationalized more accurately. More insight is needed into mobility patterns combined with behavioural insights on use of food retailers and food delivery services and perceptions of the food environment. This can be done by detailed assessment to these environmental exposures over time in relatively smaller longitudinal observational studies that account for other exposures than the residential environment and activity space of individuals. These studies can contribute to a more accurate exposure assessment in cohort studies or registries to investigate the association with incidence of type 2 diabetes. The exposure assessment in cohorts could be improved using regression calibration techniques when necessary data are available. Otherwise, assessment should be improved by incorporating relevant exposure measures in follow-up questionnaires. For the social environment, future research should account for methodological challenges in investigating the link between social environment and type 2 diabetes risk, such as inconsistent conceptualisations of the social environment; measurements unable to tease apart different social phenomena operating at multiple levels of influence; long time lag between exposure and impact on type 2 diabetes development; and risk accumulation over the life course (59, 112, 113).

For green space, walkability, air pollution and neighbourhood socioeconomic position, consistent and robust associations with type 2 diabetes have been documented. For these aspects, structural interventions should be evaluated on their effect on risk of type 2 diabetes and other chronic diseases using health impact modelling or natural experiments. These studies will contribute to urban planning and help shape a healthier living environment

Conclusion

In conclusion, our environment accounts for a substantial proportion of disease burden due to type 2 diabetes. Studies have provided consistent evidence that air pollution, residential noise, neighbourhood walkability, green space and area-level socioeconomic deprivation are associated with risk of type 2 diabetes. Current evidence on the contribution of the food environment, other aspects of the social environment and temperature is low or inconsistent. Our environment is thought to affect risk of type 2 diabetes mainly through mechanisms incorporating lifestyle factors such as physical activity or diet, the microbiome, inflammation or chronic stress. Future studies should focus on investigating the longitudinal association of changes in our environment in relation to risk of type 2 diabetes and whether these associations are explained by these proposed mechanisms. When robust evidence on the association of environmental factors with risk or type 2 diabetes is available, natural experiments or health impact modelling can help to evaluate the impact of environmental interventions on disease burden. This will contribute to urban planning and help shape a healthier living environment.

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