CHAPTER 1

General introduction
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With currently 463 million cases worldwide, diabetes is one of the most prevalent chronic diseases (1). The majority (>90%) of all diabetes cases are type 2 diabetes (T2D) (2), a disease which may come with severe co-morbidities and long (chronic) disease trajectories. Therefore, T2D is a major public health challenge with high individual disease burden as well as societal health care costs and welfare costs (2, 3). Key modifiable risk factors for T2D are a lack of physical activity (PA) and an unhealthy diet. Socio-ecological models suggest that these lifestyle behaviours and T2D risk are shaped by individual and contextual – or environmental – characteristics. However, how environmental characteristics are associated with lifestyle behaviours and T2D risk is not clear yet, and therefore this thesis aims to investigate 1) the association between food environment, diet quality and T2D outcomes and 2) the association between PA environment, PA behaviours and T2D outcomes.

In this introductory chapter I will briefly describe T2D as a major chronic disease and the potential of lifestyle behavioural modifications to help prevent and manage T2D. Then, I will discuss determinants of these lifestyle behaviours according to socio-ecological models, and elaborate on the main exposure in this thesis: the built environment. I will further discuss the association of the food environment and PA environment with T2D, and the research gaps to be addressed in this thesis.

1.1 Type 2 diabetes

Individuals are diagnosed with diabetes when blood glucose levels are chronically elevated. Diabetes originates from either a lack of insulin production in the pancreas (type 1 diabetes) or a relative lack of insulin sensitivity, i.e. insulin resistance, of the muscles to regulate glucose uptake (T2D). Prediabetes, or intermediate hyperglycaemia, is a stage preceding T2D and indicates chronically elevated blood glucose levels below the T2D thresholds. Prediabetes is associated with increased risk of T2D, but many people reverse to normoglycaemia with adequate lifestyle changes (4). Many established risk factors for T2D are non-modifiable, such as age and genetics, while others are potentially modifiable, such as overweight, unhealthy diet and lack of PA (2, 3). Other, more recently recognised, modifiable risk factors for T2D are stress and disturbed sleep (5), which will not be a main focus of this thesis. While about
10% of cases are attributed to non-modifiable risk factors, the vast majority of T2D cases can be attributed to modifiable risk factors (6). Changing these risk factors is therefore crucial to prevent T2D, but also to prevent microvascular complications in those who already have T2D, such as retinopathy, nephropathy, and neuropathy, as well as macrovascular comorbidities, such as ischemic heart disease, peripheral vascular disease and cerebrovascular disease (3, 7-10).

Several large diabetes prevention trials provided proof of concept by showing that a change in lifestyle behaviours in high risk populations, namely people with prediabetes, can substantially decrease the chance of progression to T2D (4). The Finish Diabetes Prevention Study (DPS), US Diabetes Prevention Program (DPP) and the Dutch Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM) demonstrated a 58% risk reduction after 3-years follow-up, with an intensive diet and exercise program (11-13). Such risk reductions are about twice as large as obtained by preventive use of glucose lowering medication. These results were obtained in experimental, well-controlled, settings, in high-risk populations and provide strong and convincing evidence for the potential of lifestyle modification for T2D prevention.

However, a translation of such interventions to real-life, less-controlled, settings is challenging (14). Overall, reduced effectiveness is observed even in the well-controlled settings when follow-up time increased (e.g. in the DPS after 2 years 58%, and after 6 years 15% risk reduction) (15). Moreover, real-life contextual factors, such as behaviours of family, friends, colleagues, availability of healthy food retailers or active transport opportunities, are not taken into account in well-controlled settings, while such factors can enhance or inhibit lifestyle behaviour change. These contextual factors may be key for lifestyle behaviour modifications to be successful in the long term. In addition, due to the high number of individuals at high-risk, it has become very challenging to reach everyone with intensive individual-level lifestyle behaviour change programmes. In addition, a focus on the overall population could be more effective for population-level T2D prevention. As the famous epidemiologist Geoffrey Rose already argued that in prevalent disease “a large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk” (16). Following this reasoning toward prevention, means that small reductions in exposure for the whole
population may reduce population morbidity more than targeting only the high-risk individuals with rigorous treatment or interventions. In the context of T2D prevention, this leads to the question, what is a lifestyle behaviour and what determines whether people engage in healthy or unhealthy lifestyle behaviours?

1.2 Determinants of lifestyle behaviour

Socio-ecological models posit that individual behaviour is influenced by a range of *intra-individual behavioural determinants* in the biological and psycho-social domains, and that these determinants are influenced or moderated by different layers of more upstream determinants, including *inter-individual determinants* (or social environment), *physical environment*, and *policy environment*, that together influence lifestyle behaviours (Figure 1).

*Intra-individual determinants* can be biological determinants, such as age, sex, height, weight, body composition, and (other) hereditary factors, or psycho-social determinants, such as motivation, intention, attitude, subjective norm, self-efficacy, anticipated regret, risk perception and knowledge (17). Traditionally, lifestyle programmes have a strong focus on changing these intra-individual psycho-social behavioural determinants (14, 18, 19). However, socio-ecological models suggest that behaviour is also influenced by facilitating and enabling characteristics of upstream determinants (20). *Inter-individual determinants* consist of factors in an individual’s social network, which may include family members, friends, neighbours, colleagues.
et cetera. *Physical environmental determinants* consist of a broad range of ‘what is available and accessible’ in the environment, such as PA and dietary resources in one’s environment at different levels, such as food choices in a workplace cafeteria or in the home, to the availability of opportunities for PA and healthy diet in neighbourhoods (man-made), the latter is also referred to as the built environment (21, 22). The *policy environment* can have an influence on lifestyle behaviours through laws and regulations, for instance by taxing sugar-sweetened beverages (17). In this thesis, the focus will be on the role of the physical environment, and more specifically the built environment, and how it relates to lifestyle behaviour and T2D.

**1.3 What is the built environment and how is it related to health?**

The built environment is defined as “the totality of places built or designed by humans, including buildings, grounds around buildings, layout of communities, transportation infrastructure, parks and trails” (23). Often implications of intervening in the built environment seem distal to individual’s health status, but according to Rose’s theory can be most influential for population health (16). An example where intervening in the built environment caused a major public health benefit, was the development of sanitation systems in the 19th century after outbreaks of infectious diseases in urban areas (24).

With regard to changing lifestyle behaviour for T2D prevention, the neighbourhood built environment as a potential risk factor for T2D development is still underexplored. Several systematic reviews have been conducted on associations between built environmental characteristics and cardiometabolic outcomes, but only few of the included studies investigated T2D as an outcome (25, 26). A research agenda published by Leal and Chaix (2011), indicated that more studies should be performed with T2D as an outcome (26). The built environment with regard to T2D prevention can be subdivided in two main dimensions: 1) food environment (e.g. proximity to supermarkets, density of fast-food outlets), 2) PA environment (e.g. transport-related, leisure, such as proximity to green space and recreational facilities). These domains are present in built environments with a more urban or rural character, which is often defined by residential density.
1.3.1 **Urban and rural**

Urbanisation is the increase of the population proportion residing in cities, and contributes to a shift in population exposures to factors that affect health, for instance through food options, transport, air pollution, and noise (27). Rapid increases in urbanisation and consequent changes in lifestyle behaviours in the past decades were paralleled by rising obesity and T2D prevalence/incidence (3). In estimations of the United Nations, the population in cities will further increase from 50% to 70%, worldwide over the next 20 years. Models presented by the International Diabetes Federation in 2015 indicate that T2D in urban areas will almost double between 2015 and 2040, while in rural areas this rise is expected to be much less rapid (about 12%). It is therefore important to understand the impact of urbanisation on T2D risk, in order to create healthy cities.

1.3.2 **Food environment**

The food environment refers to the availability of healthy foods and is often categorised in five dimensions: availability, accessibility, affordability, acceptability, and accommodation (28). The first two dimensions are physical or geographical measures: availability is the presence of food outlets, and accessibility refers to the location of food outlets. The latter three refer to economic values (e.g. food pricing), social norms (e.g. attitude, advertising) and adaptation to resident’s needs (e.g. store opening hours).

Higher availability of energy dense foods and convenience foods may lead to higher consumption of these unhealthy products. Subjective measures of the food environment, such as perceived availability of healthy foods, have been associated with higher diet quality (29). Research using objective geographical measures are far less consistent (29). Greater availability of fast food outlets has been associated with lower neighbourhood SES, and with lower fruit and vegetable consumption (30). Associations between the food environment and health outcomes, such as obesity, have been very heterogeneous (30, 31). Studies that investigated the food environment in association with T2D incidence, such as the Multi-Ethnic Study of Atherosclerosis (MESA), indicated that perceived availability of healthy foods was associated with lower T2D incidence, but these findings could not be reproduced with objective measures of the built environment in this longitudinal setting (32). The association between objective geographic measures of the food environment and T2D incidence
is understudied and poorly understood, and therefore opportunities exist in exploring this association with high quality geographic data linked to individual-level T2D.

1.3.3 Physical activity environment

The built PA environment can be different depending on the domains of PA: leisure and transport. The presence of parks or leisure facilities could enhance leisure PA, and availability facilitating infrastructure can enhance active transport. Transport systems have the potential to influence health not only through PA, but also through associated exposures such as air pollution, noise, and traffic safety (27). From a planning and transport perspective the physical environmental influences on travel can be classified in the 6 Ds: density, diversity, design, destination accessibility, distance to transit and demand management (33). Where density indicates density of population, services, or jobs. Diversity refers to heterogeneous land uses (i.e. residential, retail, recreational and industrial areas), often expressed in land-use mix. Design includes infrastructure elements, such as connectivity, road types and intersections. Destination accessibility is often expressed as a distance to a destination, or destination characteristics that influence accessibility, e.g. parking opportunity at work. Distance to transit indicates the spatial accessibility of public transit stops and stations. Demand management refers to indicators of how travel demand is managed by features or policy, such as parking supply and cost (33).

Composite measures of the built PA environment have gained attention, because of analytical advantages. An example of such a composite measure is neighbourhood ‘walkability’, which has been associated with higher levels of PA in multiple studies (34, 35). A walkability index is usually constructed of three factors: population density, land-use mix, and connectivity. Low walkability is also consistently associated with more obesity, although mainly in North-American settings (31), and with T2D in some studies (36). Opportunity for further explorations on the built environment and shifting passive to active transport through built environment are yet to be made. For instance, studies on walkability focus on small residential areas, although someone’s activity space often goes beyond the residential area, and there may be other reasons (individual reasons such as age, safety or household composition) to choose passive modes of transport. This opens opportunities to investigate how built environment influences passive transport choices, and which determinants may be most important.
in this decision. Additionally, the role of the somewhat more established positive
built PA environment characteristics, such as walkability, are not yet well explored in
populations with T2D. Only few studies investigated this association in this population,
and only with self-reported measures of the built environment (37-39).

1.4 Built environment and diabetes research – research gaps

The association between built environment characteristics and T2D is a relatively new
area of research. A recent systematic review on built environment and cardiometabolic
outcomes indicated that publications with T2D as outcome started to appear from
2001 onwards, with a total of nine publications on this subject in 2009 (26). Little
research has been done on T2D, compared to other health outcomes, such as obesity
(106 publications between 1998 – 2009) and hypertension (27 publications between
1988 – 2009). In the available literature to date on the association between the built
environment and T2D (and other health outcomes), some methodological research
gaps can be identified. Generally, these gaps regard aspects related to measurement,
study designs, and analytical approaches.

1.4.1 Measurement

Objective exposure measures of the built environment can be obtained by importing
spatial data sources (census, audits, google maps) into Geographic Information
Systems (GIS). The spatial data is related to participant locations (e.g. postal codes,
GPS locations) to obtain individual exposure measures, such as distance to the
closest fast-food outlet, the presence of sidewalks, or density of recreational facilities.
Such exposure measures can then be used to investigate associations with health
behaviours or health outcomes. However, exposure to the built environment is a
complex combination of interrelated characteristics, rather than a collection of such
isolated features. Therefore, the use of composite measures to reflect combinations of
built environmental characteristics has gained increasing attention (40). Examples for
PA environment composite measures are indices such as land-use mix and walkability,
and for the food environment a relative food environment index (RFEI) was developed.
Land-use mix and walkability has been consistently associated with PA behaviours
and obesity (26, 31). This overview is not yet available for food environment, but for the RFEI and T2D mixed results are observed (36, 41). Review studies have indicated that these composite measures should gain more attention, as these capture the interrelated character of the built environment, reduce spatial collinearity and enhance interpretation and communication of results (40).

In addition to objective measures, the subjective environment, i.e. how one sees or perceives one’s environment, may also influence one’s motivation and perceived opportunities to eat healthily or be physically active, as posed in socio-ecological models. Subjective environmental measures are considered as more individual-level based. However, objective measures are generally and intuitively preferred, as they indicate what is available in the environment, whereas subjective measures indicate what is perceived to be available and perhaps how the built environment is used. Subjective measures are frequently used in built environment research (42), but seem to suffer from self-report bias. To investigate such discrepancies, it is useful to investigate self-reported environmental exposures, next to objective GIS measured in the same population. This requires a specific combination of measurements (26, 42). For example, the MESA study found an inverse association between self-reported healthy food environment and T2D incidence, but this inverse association was not found with the GIS-based measure of healthy food environment (32). This difference in associations for subjective and objective measures was also observed for PA environment and PA, although this was sometimes because both methods measured a different construct of the environment (e.g. objective recreational facilities and subjective walking infrastructure), probably due to data availability limitations. To improve studies into the association of subjective and objective exposure to the built environment with T2D, this requires a targeted data collection to investigate the combination of both.

1.4.2 Study design and analytic approaches

To date, most studies on built environment and T2D have used cross-sectional and ecological designs (26, 42). A hierarchy of level of evidence for causal relationships within epidemiological research has been defined based on the study design, sometimes visualised as a pyramid (43, 44). For the built environment and T2D, most studies used research designs from the lower levels of the pyramid, and thus the use
of stronger research designs leading to stronger evidence for (lack of) association is needed. However, strong research designs such as randomised trials are mostly not feasible in built environment research, as one cannot randomise participants over environments, let alone do this in a double-blinded manner. Therefore, to gain more meaningful insight into associations, (prospective) cohort studies are needed to investigate associations between built environment and incidence of T2D, using appropriate analyses methods (42). Even though the use of such prospective designs would be a step forward in the field, these designs still suffer from confounding and residential self-selection bias, limiting conclusions on causality. Moreover, as health is a distal outcome of the potential impact of built environment, studies heavily rely on intermediates, such a lifestyle behaviour, in the association. Because the outcome is so distal, it is important to perform hypothesis-generating studies on each path, exposure to intermediate and intermediate to outcome, to assure a solid hypothesis for further research. A next step is to investigate the whole path in the same sample, to test whether the mechanism is confirmed. In present studies, however, if such intermediates are investigated, they are often simply included as covariates in the statistical models (to assess the attenuation of the association), making it difficult to disentangle the mediating pathways. Formal mediation analyses may help to investigate putative pathways, and thereby gain better insights in such pathways. Mediation analysis is a statistical method that is commonly used to unravel pathways of intervention effectiveness in RCTs, i.e. to assess whether the treatment effect was achieved through the hypothesized intervention mechanisms (45, 46). Also, in prospective studies, that unlike RCTs suffer from confounding, mediation analyses can deconstruct associations in several paths, and thereby disentangle mechanisms of the observed association. Not only can mediation analyses provide insight into observed associations, it can also help to understand null associations by indicating where associations are present, cancelled out, or consistently null (46).

1.5 Objectives and thesis outline

The main aim of this thesis is twofold: 1) to investigate the association between food environment, diet quality and T2D, and 2) to investigate the association between PA environment, PA and T2D.
More specifically, this aim is broken down into the following research questions:

1) Which built environmental characteristics potentially associated with lifestyle are consistently linked to T2D in the scientific literature?
2) How can composite and objective measures of the built environment, combined with individual characteristics, improve our understanding of the built PA environment in the association with T2D?
3) What are mediating pathways between built environments potentially related to PA and diet and T2D outcomes?

1.5.1 Outline of this thesis
This thesis consists of three parts. The first part includes a general overview of all evidence on the built environment and T2D to date. The second part includes research on main aim 1: the association between the food environment, diet quality and T2D. The third part includes research on main aim 2: the association between PA environment and T2D.

Part I: Current evidence

Chapter 2 provides an overview of the available evidence to date on built environmental characteristics, potentially associated with the lifestyle behaviours, and incidence or prevalence of T2D based on a systematic review and meta-analysis.

Part II: Food environment, diet quality and T2D

Chapter 3 describes the association between adherence to the new Dutch Dietary guidelines of 2015 and incidence of prediabetes and T2D, using data from the harmonised Hoorn Study cohorts. Both cohorts were similar in design, with baseline food frequency questionnaires and high quality prediabetes and T2D incidence measurements after ~7 years of follow-up.

Chapter 4 describes the association between spatial accessibility of food retailers and incidence of T2D in the Netherlands, and whether the association is mediated
by adherence to the Dutch Dietary guidelines of 2015. Data from the Geoscience
and Health Cohort Consortium (GECCO) were used (47), aiming to link objective
geographical data sources across The Netherlands to individual-level prospective
cohort data. Four cohort studies were selected (from a total of 21), that included
baseline and follow-up diabetes measurements after 2004, and linked to field audit
retail data.

Part III: physical activity environment, physical activity and T2D

Chapter 5 describes the association of individual and built environment characteristics
with car use across Europe, using data from the Sustainable Prevention of Obesity
Through Integrated Strategies (SPOTLIGHT) study, a cross-sectional study conducted
in five European countries with harmonised geographical data (48).

Chapter 6 describes the development and validation of a composite drivability index.
This index is developed to capture how conducive areas are to car use, in the City
of Toronto. For this chapter we used open source GIS data to create the index, and
transport outcomes and covariates were used from the cross-sectional Transportation
Tomorrow Survey, a community survey with a sample of over 60,000 participants in
2016 to validate the index.

Chapter 7 describes the association between neighbourhood walkability and T2D
progression in the Netherlands, and whether this association was mediated by PA. For
this chapter we used data from a subsample of the Diabetes Care System (DCS) cohort,
where additional measurements on self-reported built environment, diet (FFQ) and
PA (accelerometry) was collected in 1,549 participants in 2017-2018. The DCS includes
12,673 patients with diabetes for annual medical visits, in the region West-Friesland (49).
References


