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## Diet, Inflammation, Body Composition and Type 2 Diabetes: Insights from epidemiological studies

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# General Introduction



## INTRODUCTION

### Type 2 diabetes

Type 2 diabetes, a metabolic disorder characterized by elevated serum glucose levels and reduced sensitivity to insulin, has become a worldwide public health concern. The prevalence of this disease has risen sharply during the last decades. In 2014, it was estimated that approximately 8.5% of adults suffer from type 2 diabetes globally.<sup>1,2</sup> Aside from symptoms directly related to disturbances in glucose metabolism, type 2 diabetes can cause severe long-term cardiovascular complications if not carefully managed.<sup>1</sup> These potential complications include myocardial infarction, stroke, peripheral arterial disease and blindness.<sup>2</sup> Due to its high prevalence and serious complications, type 2 diabetes accounts for a substantial economic and healthcare burden worldwide.<sup>3</sup> The healthcare costs related to type 2 diabetes are projected to have risen even further by the year 2030, in parallel with an ever increasing prevalence of the disorder in the coming decades if the present trend continues.<sup>4,5</sup>

### Diet

The marked increase in the prevalence of type 2 diabetes is, amongst other factors, attributed to increasing rates of obesity, decreased time spent in physical activity in favor of sedentary time and the consumption of increasingly unhealthy diets.<sup>2</sup> The relationship between aspects of the diet and risk of type 2 diabetes appears to be especially complex. Diet may affect risk of type 2 diabetes through its effects on body weight, but dietary factors may also affect risk of the disease independently of body weight.<sup>6</sup> Several different approaches have been used to study the relation between diet and type 2 diabetes. For instance, at the level of individual nutrients, it has been suggested that higher intake of magnesium, vitamin C and carotenoids provide a lower risk of type 2 diabetes.<sup>7-9</sup> With regards to food groups, it appears that lower consumption of vegetables, fruits and whole grains and higher consumption of red meat and sugar-sweetened beverages increase type 2 diabetes risk.<sup>6,10</sup> Considering dietary patterns as a whole, a Mediterranean-type diet, which is characterized by a high consumption of fruits, vegetables and legumes as well as moderate intake of fish and abundant use of olive oil, is associated with lower long-term risk of type 2 diabetes.<sup>11-13</sup> The many different approaches that have been used in studying diet as a determinant of type 2 diabetes highlight that this is a complicated field of research in which many questions remain unanswered. Notably, the mechanisms of action through which aspects of the diet may affect type 2 diabetes risk are subject to debate and may include effects on body composition and chronic low-grade inflammation.

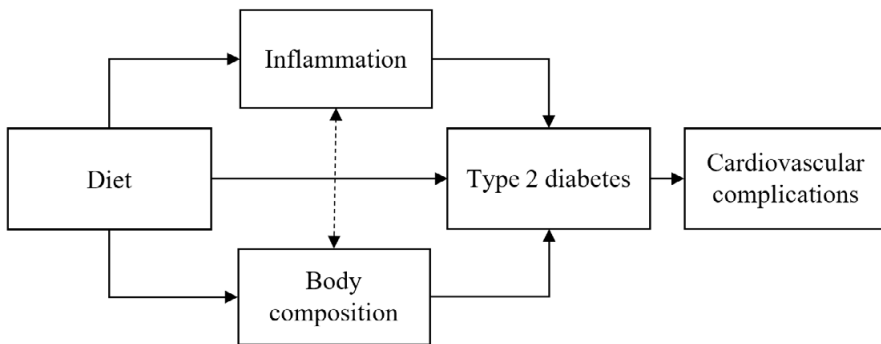
## Body composition

Given that obesity is one of the most firmly established risk factors for type 2 diabetes and its complications, one of the primary pathways through which diet may play a role in diabetes prevention is through inducing weight loss or preventing weight gain.<sup>6,14</sup> Although body weight is an important and frequently used parameter in this regard, more recent research has demonstrated that body weight and its simple derivatives such as body mass index (BMI) provide an incomplete picture of an individual's body composition due to the fact that BMI fails to differentiate between fat mass (adipose tissue) and lean mass (non-adipose tissues).<sup>15,16</sup> It has been shown that whereas higher fat mass is associated with increased risk of all-cause mortality, increases in lean mass generally confer a lower mortality risk.<sup>17</sup> Similarly, whereas higher lean mass is associated with lower risk of metabolic syndrome, higher fat mass is positively associated with metabolic syndrome.<sup>18,19</sup> The notion that body composition provides more information with regards metabolic disturbances than BMI is underlined by the observation that increased visceral fat mass is associated with increased insulin resistance, whereas increased subcutaneous fat mass may decrease insulin resistance.<sup>20</sup> Thus, not only the absolute quantity of fat mass but also its physical location has important metabolic implications, and BMI alone fails to capture this distinction. These differential effects of visceral and subcutaneous fat mass may be explained by differing inflammatory responses to excess adipose tissue in different locations.<sup>21</sup> Therefore, while the relation between obesity and type 2 diabetes may appear straightforward at first glance, much more is at play on a metabolic level. In line with this, diet may not only affect body weight but also body composition through effects on specific fat depots.<sup>22</sup>

## Inflammation

Another pathway through which aspects of the diet may affect risk of type 2 diabetes is through systemic low-grade inflammation. Inflammation is a physiological process characterized by the release of mediators such as cytokines and chemokines in response to stressors, and is a critical feature of the immune system which helps maintain or reinstate homeostasis in the presence of tissue damage.<sup>23</sup> However, a persisting inflammatory response without an apparent trigger can also occur and is often regarded as detrimental to metabolic functioning.<sup>23,24</sup> Such an extended period of low-grade inflammation can be caused by the consumption of specific nutrients or a state of metabolic surplus as occurs in case of obesity.<sup>25</sup> With regards to metabolic surplus, the notion that inflammatory mediators are more abundantly expressed in obese individuals as opposed to lean individuals is commonly accepted.<sup>26</sup> A wide range of nutrients may have pro-inflammatory effects, although untangling the many pleiotropic effects these individual nutrients may have on inflammation *in vivo* has proven

challenging.<sup>27</sup> On a macro level, adherence to a Western-type dietary pattern (characterized by high intake of processed meat, refined grains and high-fat dairy, amongst other factors) is associated with elevated markers of inflammation.<sup>28,29</sup> Regardless of the exact source of the inflammatory process, inflammatory mediators such as tumor necrosis factor (TNF) may increase risk of type 2 diabetes through interfering with insulin signaling.<sup>30</sup> Interestingly, experimental evidence has indicated that this disruption of insulin signaling due to inflammation also takes place in the absence of overt obesity.<sup>25</sup> The prominent role of inflammation in the pathogenesis of obesity and insulin resistance has given rise to the idea that type 2 diabetes is, at its core, an inflammatory condition.<sup>31</sup> The importance of the concept of inflammation with regards to disease onset, as well as the notion that diet may be an important instigator of inflammation, emphasizes the importance of research linking diet to inflammatory processes.



**Figure 1.1.1.** Proposed relation between determinants of type 2 diabetes and its eventual complications.

## Thesis outline

Given that diet, body composition and inflammation are closely interwoven, disentangling how these factors interact with each other in the context of the pathogenesis of type 2 diabetes has proven no small feat. A framework for conceptualizing how they are related is displayed as Figure 1.1.1. With this thesis, I aim to further clarify how these factors are interrelated and affect risk of type 2 diabetes. The majority of the work contained in this thesis was performed within the Rotterdam Study, a large population-based cohort of approximately 15,000 participants. A number of the studies in this thesis were also performed within the United Kingdom (UK) Biobank, an open access cohort study of over half a million participants. As such, I approach the topics from an epidemiological perspective. The second chapter of this thesis is focused on dietary factors in relation to type 2 diabetes. In chapter 2.1, we investigate the relation

between total dietary antioxidant capacity and insulin resistance as well as risk of type 2 diabetes. In chapter 2.2, we examine the association between a plant-based diet and insulin resistance as well as incidence of prediabetes and type 2 diabetes. In the third chapter we discuss markers of inflammation and their relation to prediabetes and type 2 diabetes. In chapter 3.1, we examine uric acid in relation to risk of these outcomes. Following up on this, in chapter 3.2, uric acid is investigated in relation to risk of fatal and non-fatal cardiovascular events. In chapter 3.3, we study the role of C-reactive protein as a mediator in the association between coffee consumption and risk of type 2 diabetes. In the fourth chapter we address body composition and investigate its dietary determinants. In chapter 4.1, total dietary antioxidant capacity is investigated in relation to longitudinal patterns of body composition. Finally, in chapter 4.2, we explore the association between consumption of dietary advanced glycation end-products and body composition. In chapter 5, I provide an overview of the major findings from this thesis, discuss relevant methodological considerations and reflect on the implications of our work as well as potential directions for future research.

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