Chapter 1

General introduction

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1.1 Cardiovascular disease

Cardiovascular disease, including coronary heart disease and stroke, is becoming increasingly prevalent worldwide (1). Cardiovascular mortality accounted for 31% of all global deaths in 2015 (2). Cardiometabolic risk factors, such as obesity, hypertension, dyslipidemia and diabetes, lead to higher rates of cardiovascular disease and cardiovascular mortality (3). Cardiovascular disease is currently the leading cause of death among women (Figure 1), and unrecognized or undiagnosed cardiovascular disease presentations in women may play a role in the high mortality rates (4). Smoking is an established risk factor for development of cardiovascular disease, and differences in smoking behavior between men and women have decreased over time (5). Obesity is one of the most prevalent risk factors of cardiovascular disease, with rising trends especially among women (3). In the Netherlands almost half of the adults are overweight (body mass index (BMI) ≥ 25 kg/m^2), and 14% of the adults are obese (BMI ≥ 30 kg/m^2) (6). Among Dutch women of reproductive age the prevalence of overweight and obesity was 40% and 13% respectively, in 2017 (7). Obesity not only has a major impact on physical health, it also impairs mental health: obesity increases the risk of the development of depressive symptoms, anxiety and it impairs quality of life (QoL) (8, 9). In addition, obese individuals report higher levels of stress and lower sleep quality (10, 11). In turn, impaired mental wellbeing and sleep increase the risk of weight-gain and subsequent cardiovascular disease, suggesting a vicious cycle (12-14).

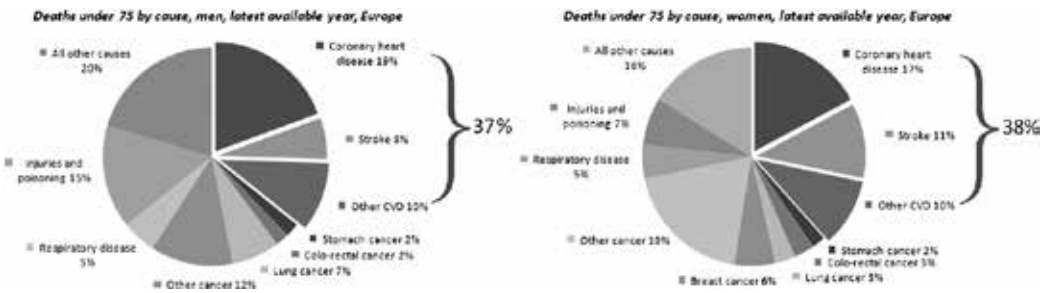

Figure 1. Deaths by cause in men and women in 2012, adapted from Appelman et al (15).

Early life origins of obesity

Not only unhealthy lifestyle factors are an important cause of obesity, such factors include excess intake of high energy and high-fat foods and physical inactivity (16, 17), also the pre- and postnatal environment determines individual sensitivity to environmental factors and risk of obesity. The developmental origins of health and disease hypothesis (DoHaD) proposed by David Barker states that exposure to an unfavorable environment during prenatal development programs changes in the fetus (18, 19). Prenatal programming effects may ultimately lead to increased rates of disease in adulthood (19). For example, low birth weight, together with infant catch-up growth is associated with increased risk of obesity in adulthood (20). Maternal obesity has also been linked to offspring obesity and cardiovascular disease later in life (20, 21). Additionally, prenatal programming has been observed for maternal depression, anxiety or the death of a relative or friend during pregnancy and may lead to developmental, physical and mental alterations in the offspring (22). These alterations in the offspring include structural malformations, reduced birth weight, behavioral problems and depression and anxiety in adolescence and adulthood (23, 24).

High sensitivity to the environment is not only present in the prenatal and early postnatal period, but also during childhood (25). Early life adversity is linked to impaired physical health and mental wellbeing in later life (26, 27). Early life adversity may consist of traumatic experiences during childhood, such as physical and sexual abuse, loss of a parent, or exposure to domestic violence, but also of chronic stress prenatally or during childhood, including parental mental illness, parental neglect and maternal depression during pregnancy (23, 28). While early life adversity includes prenatal adversity, childhood adversity is defined as postnatal traumatic experiences or chronic stress during childhood. In the Netherlands, the prevalence of having experienced at least one adverse event in childhood is approximately 40%, and of those events emotional neglect was the most prevalent (29, 30). Early life adversity, may lead to a 1.5 fold increased risk to be severely obese in adulthood (BMI ≥ 40 kg/m^2) and increases the risk of adult depression, cardiovascular disease, cancer, and even mortality (26, 31-34).

Early life adversity and cardiometabolic mediation effects

The association between early life adversity and poor cardiometabolic health outcomes may be mediated by cognitive impairment, poor health behaviors, impaired mental wellbeing and/or negative personality traits in adulthood (Figure 2). People exposed to childhood adversity have lower cognitive ability (35), are

more often smokers in adulthood (36), have a preference for unhealthy food (37), experience more depressive and anxiety symptoms (27), more post-traumatic stress symptoms (27), and have more neurotic and socially inhibited personalities (38, 39). All of these factors are also linked to poor cardiometabolic health (40-44).

Figure 2. Early life adversity effects across the lifespan, adapted from Felitti et al (32).

Effects of early life adversity on the HPA-axis

Early life adversity may also be linked to negative health outcomes and mental wellbeing in adult life through stress, since early life adversity is associated with increased levels of stress (33), and high levels of stress are linked to impaired physical health (26). Altered functioning of the hypothalamic pituitary adrenal (HPA) axis has been proposed as an important mechanism linking early life adversity and impaired physical and mental health (45, 46). The HPA-axis is one of the major stress systems in the body and responds to physiological and psychological stress. The hypothalamus produces corticotrophin-releasing hormone (CRH) in response to stress, which stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH), resulting in increased production of cortisol, a neuroendocrine glucocorticoid hormone released from the adrenal cortex. This cascade of system activation and hormone release enables the body to meet demands in response to stressors. For example, cortisol increases blood sugar and suppresses the immune system which may be adaptive in such a way that the body meets the demands of the stressful environment. The body prioritizes energy availability needed in case of action, over immune system activation. However, prolonged HPA-axis activation may lead to long-term exposure to high levels of cortisol, which may no longer be adaptive and increases the risk of obesity, high blood pressure, hyperglycemia and

unhealthy cholesterol levels (47-49). Besides negative effects of increased cortisol levels on physical health outcomes, effects on mental health symptoms have been described as well, including depression and anxiety (50, 51).

Together with cortisol, the adrenal glands release the steroid dehydroepiandrosterone (DHEA). The co-release of DHEA with cortisol seems to have a protective effect against the blood sugar increasing properties of cortisol, although the molecular mechanisms by which DHEA protects are largely unknown (52). Previous research suggests that early life adversity is not only associated with increased cortisol release, but may also be linked to altered DHEA levels (53). In research, DHEA is often measured in relation to cortisol levels, and reported as DHEA/cortisol ratio, in which low DHEA levels in relation to cortisol levels may provide less protection against the negative effects of long-term increased cortisol exposure. Associations between early life adversity and both increased and decreased levels of DHEA have been reported, which may be linked to behavioral and cognitive problems in childhood and adolescence (53, 54).

The other major system involved in stress responses is the autonomic nervous system (ANS). This largely unconsciously acting system regulates an acute response to stress including increased respiration rate and heart rate. During the acute stress response ANS activation has an adaptive function, such that the body is prepared to meet demands necessary in fight or flight reactions. Early life adversity has been linked to both increased and decreased, and potentially maladaptive, ANS functioning, leading to abnormal heart rate responses to stress in childhood and adulthood (55, 56). Autonomic imbalance as a result of early life adversity may lead to an increased risk of cardiovascular disease in adulthood (57).

Lifestyle interventions

Lifestyle intervention in individuals at increased risk for cardiovascular disease development, as a result of early life adversity and/or unhealthy lifestyle factors, is important to reduce the risk of cardiovascular disease and early death. In order to reduce weight and the associated negative effects on mental wellbeing and cardiometabolic risk, in persons who are overweight or obese, lifestyle interventions are advised as the first step in the treatment of overweight and obesity. A meta-analysis assessing the effectiveness of lifestyle interventions aimed at weight loss and improvement of cardiometabolic health has shown that lifestyle adjustments are difficult and weight loss results are disappointing (58), although more recent evidence suggests lifestyle interventions aimed at prevention of diabetes type 2 are effective in inducing long-term weight loss (59). Individuals who are highly

motivated to change lifestyle may be more successful in lifestyle adjustments and losing weight (60). Timing and duration of the intervention could play an important role in the effectiveness. For example, women are particularly receptive to lifestyle guidance in the preconception period. This was illustrated by smoking cessation numbers that are almost eight times higher in women trying to conceive, compared to women not trying to conceive (61). To reduce overweight and obesity, and the related impaired cardiometabolic and mental health outcomes, it is important to explore the effectiveness of preconception lifestyle interventions, not only for the women involved but also for the health of their offspring. A preconception lifestyle intervention may not only improve the cardiometabolic and mental health of the participants themselves, but could potentially improve the prenatal environment and health of the offspring (62). As described above, the prenatal environment is linked to long-term physical and mental wellbeing, and an improved prenatal environment could potentially decrease the risk of cardiovascular disease in adulthood (62).

The LIFEstyle study is the first large randomized controlled trial (RCT) assessing the effectiveness of a preconception lifestyle intervention among obese infertile women (63). This study provides unique information regarding the effects of preconception lifestyle intervention on women's fertility, as well as on cardiometabolic health and mental wellbeing of the participating women and their offspring.

Childhood adversity and intervention effectiveness

Lifestyle adjustment has proven to be difficult and lifestyle interventions have been associated with partial weight regain (58, 59). Consistent explanations for these negative results are currently lacking. Besides the possible importance of timing of the intervention, characteristics of participants could also play a role in intervention effectiveness (64, 65). Some individuals might benefit more from lifestyle interventions, because they are more receptive to lifestyle advice. It has been suggested that childhood adversity leads to unhealthy eating behavior and physical inactivity (66, 67), but also to increased susceptibility to the environment (25), and possibly increased receptiveness to advice. Individuals exposed to childhood adversity might benefit more from lifestyle interventions compared to those who were not exposed to childhood adversity.

Relevance

The worldwide obesity epidemic has profound detrimental effects on the world population, significantly reducing its health and life expectancy (3, 68). Effective lifestyle interventions could potentially decrease weight and reduce the associated cardiometabolic risks, and the preconception period could be a unique window of

opportunity to change lifestyle in women. If the preconception period indeed is a phase in life during which women are more receptive to lifestyle interventions in terms of weight loss, this could have implications for preconception care of obese women, as obese women might benefit from counselling in this period. The role of childhood adversity in the effectiveness of lifestyle interventions in those with overweight or obesity has not been studied previously, but could potentially point out a subgroup of women who benefit more from lifestyle interventions. With this information, lifestyle interventions could be tailored to participants with and without a history of childhood adversity, resulting potentially in more cost-effective and successful lifestyle interventions in order to reduce weight and cardiovascular risk.

Aim of the thesis

- The first aim of this thesis is to investigate if early life adversity is associated with poor cardiometabolic health in adulthood, and to explore potential neuroendocrine, behavioral and psychological pathways involved in this association.
- The second aim is to assess the effect of a preconception lifestyle intervention on cardiometabolic health and mental wellbeing, and if such an intervention is more effective in improving body composition in those who experienced childhood adversity.

1. Outline of this thesis

In **Chapter 2** of this thesis the association between childhood adversity and cardiometabolic health, and possible mediation through health behaviors, psychological distress, mood symptoms and personality are investigated in a cross sectional study. In **Chapter 3** the associations between maternal depression during pregnancy and HPA-axis and ANS reactivity in the offspring are systematically reviewed. In **Chapter 4** the sex-specific associations between different types of childhood adversity and levels of cortisol and DHEA in adolescence are examined in a cross sectional study. In **Chapter 5** the effects of a preconception lifestyle intervention RCT in obese infertile women on cardiometabolic health and QoL within one year are studied. In **Chapter 6** the effects of this intervention RCT on cardiometabolic health five years after the intervention are described. In **Chapter 7** the effects of the preconception lifestyle intervention RCT on levels of perceived stress, mood symptoms, sleep quality and QoL five years after the intervention are presented. **Chapter 8** describes a systematic review and meta-analysis of the effects of lifestyle interventions on symptoms of depression and anxiety among women of

reproductive age. In **Chapter 9** we assess whether the effects of a lifestyle intervention in obese infertile women on body composition, depend on their history of childhood adversity exposure. In **Chapter 10** the results from this thesis are summarized, clinical implication and recommendations for future research are presented.

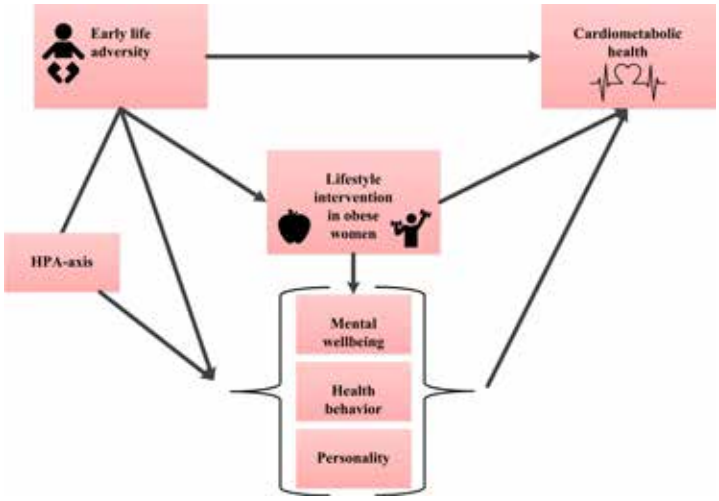

Figure 3. Model presenting the main topics and pathways described in this thesis.

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