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„The Influence of Weight Loss Interventions on Circulating Sex Steroid Concentrations in Women: a Systematic Review and Meta-analysis“

verfasst von / submitted by

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Hannah Spahits, BSc.

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Abstract

The number of overweight and obese people is increasing every year. This represents a major public health concern for our global society. These conditions are also linked to an increased risk for other diseases, such as cancer (e.g. endometrial, breast, ovarian, prostate, and colon cancer). It is not yet clear, through what mechanisms, overweight and obesity are associated with a higher risk of these cancer types. The incidence of obesity-related cancers is increasing rapidly, and it is thus crucial to better understand the underlying mechanisms, that link lifestyle factors to disease risk and find ways for prevention. This thesis focuses on the sex steroid pathway as a biologic mechanism linking overweight and obesity to cancer. We systematically review and meta-analyse studies that investigated the influence of surgical (n=14) or lifestyle (n=29) interventions on circulating sex steroids (e.g. androgens and estrogens) and Sex hormone binding globulin (SHBG) in women. Our results show, that a decrease in different anthropometric measurements, corresponding to reduced adiposity (Body mass index (BMI), weight, fat mass and % body fat) are associated with a decrease in circulating testosterone, free testosterone, estradiol (postmenopausal), free estradiol (postmenopausal) and estrone (postmenopausal) and an increase in SHBG. Evidence suggests, that an increase in testosterone and estradiol and decreased SHBG is associated with higher risk for postmenopausal breast-, endometrial- and ovarian cancer, lower levels might reduce the risk. Therefore, Our results indicate, that weight loss interventions may be a cancer prevention strategy in obese and overweight women as a result of the impact on sex steroid hormone concentrations.

Kurzfassung

Die Zahl der übergewichtigen und fettleibigen Menschen steigt von Jahr zu Jahr an. Für die globale Bevölkerung stellt das ein erhebliches Gesundheitsproblem dar. Übergewicht und Fettleibigkeit werden außerdem mit einem erhöhten Risiko für andere Krankheiten in Verbindung gebracht, darunter auch mehrere Krebsarten (z.B. Endometrium-, Brust-, Eierstock-, Prostata- und Darmkrebs). Es ist allerdings noch nicht geklärt, warum Übergewicht und Fettleibigkeit mit einem höheren Risiko für diese Krebsarten einhergehen. Da die Zahl der Betroffenen bei beiden Krankheiten rapide ansteigt, ist es von entscheidender Bedeutung, die zugrunde liegenden Mechanismen, die Lebensstilfaktoren mit dem Krankheitsrisiko verknüpfen, besser zu verstehen und Möglichkeiten der Prävention zu finden. In dieser Arbeit liegt der Schwerpunkt auf dem Geschlechtshormon-Mechanismus. Wir untersuchen systematisch und mithilfe von Metaanalysen, welchen Einfluss ein durch chirurgischer (n=14) oder Lebensstil (n=29) Interventionen erzielter Gewichtsverlust auf zirkulierende Geschlechtshormone (z.B. Androgene und Östrogene) und SHBG in Frauen hat. Unsere Ergebnisse zeigen, dass eine Reduktion von BMI, Gewicht, Körperfett und % Körperfett mit einer Abnahme an Testosteron, freiem Testosteron, Östradiol (postmenopasuale Frauen), freiem Östradiol (postmenopasuale Frauen) und Estrone (postmenopasuale Frauen) sowie mit einer Zunahme an SHBG assoziiert ist. Da es Hinweise gibt, dass ein erhöhter Testosteron- und Östradiol-Spiegel und verminderte SHBG-Level mit einem höheren Risiko für postmenopausalen Brust-, Endometrium- und Eierstockkrebs einhergehen, könnten niedrigere Konzentrationen das Risiko verringern. Unsere Ergebnisse deuten daher darauf hin, dass Gewichtsabnahme, erzielt durch eine Intervention, eine vielversprechende Strategie für die Krebsprävention bei übergewichtigen und fettleibigen Frauen darstellen kann.

Contents

List of Tables

List of Figures

1. Introduction

1.1. Motivation

The number of overweight and obese people is increasing every year (World Health Organization, 2022). These conditions are also associated with various chronic diseases. For instance, overweight and obesity have been found to be associated with a higher risk of various types of cancer. These include endometrial, ovarian, and postmenopausal breast cancer (World Cancer Research Fund/American Institute for Cancer Research, 2018b). However, it is not yet fully clear through what mechanisms overweight and obesity are associated with a higher risk of these cancer types. One likely link is through overweight or obesity-related changes in sex steroid hormone metabolism, such as estrogens and androgens, but no systematic review and meta-analysis on mechanistic pathways have been led on the topic so far. If the association between body fatness and sex steroids, as well as the association between sex steroids and cancer risk, is confirmed, this may allow for targeted approaches for cancer prevention. Therefore, the main focus of this thesis is to investigate the association between obesity and sex steroids in circulation. More specifically, the detailed focus is on weight loss and circulating sex steroid hormones.
Other primary mechanisms, linking overweight and obesity to cancer are the insulin and insulin-like growth factor-I (IGF-I) pathway, as well as inflammation (Roberts et al., 2010). This thesis is part of an ongoing large systematic literature review project, and the associations between sex steroids and cancer risk will be investigated subsequently and are beyond the scope of this project. Furthermore, the association between body fatness and insulin/insulin-like growth factor-I and inflammation will also be investigated as part of the broader systematic review project, as well as the association of those pathways with cancer risk. The cancer types the project focuses on are postmenopausal breast, endometrial and ovarian cancer.

1.1.1. Aim of the work

The cancer incidence and mortality are increasing rapidly across the globe (Sung et al., 2021). It is thus crucial to not only find strategies for prevention of the disease, but also to better understand the underlying mechanisms linking lifestyle factors to disease risk, such that targeted interventions can be considered. This research aims to make a small contribution towards achieving this goal. The goal of this thesis is to identify possible connections between weight loss and circulating sex steroids. In particular, we will investigate the following **research questions**:

- What are the effects of weight loss on circulating sex steroid hormone concentrations in women?
- In particular:

  - How does the effect differ between different sex steroids (e.g., androgens and estrogens)?
  - How does the effect differ between different types of body composition measurements?
  - How does the effect differ between various intervention types (e.g., surgical and lifestyle interventions)?
  - How does the effect differ between pre- and postmenopausal women?

1.1.2. Contributions

In this thesis, we will make the following **contributions**:

- We systematically review all the relevant data that has been published on the associations investigated.
- We meta-analyse the findings of relevant studies (separately for surgical and lifestyle interventions) and identify associations and patterns.
- We evaluate the strength of evidence linking weight loss to sex steroid hormone metabolism

1.1.3. Structure of this thesis

The next chapters will be structured as follows:

- In **Chapter 2**, we provide an overview of the theoretical background relevant for this thesis. We provide information about the prevalence and definition of overweight/obesity and investigate the possible connection between overweight and obesity, and endometrial, ovarian, and breast cancer risk. Furthermore, we focus on describing the sex steroid pathway that is likely to be a link between body fatness and cancer.
- In **Chapter 3**, we provide a detailed description of the methods we used to conduct this meta-analysis. This includes information on the methodology for our literature search and screening, data extraction, cleaning, and analysis, and quality assessment of the analysed studies.
- In **Chapter 4**, we present an overview of the studies included in our data set and our results of the conducted meta-analysis. We will show the results of all investigated sex steroids, separately for surgical and lifestyle interventions. Furthermore, we will describe identified studies, that were not amenable to meta-analyse.
- In **Chapter 5**, we describe and discuss our primary findings. We also point out the contributions of this thesis and highlight the strengths and limitations of our approach. In addition, we provide suggestions where future research is necessary.

2. Background

In this section, we will discuss the background of the topics relevant for this thesis. First, we describe the prevalence, definition, and classification of overweight and obesity, and its effect on health. Then, we will focus on the link between obesity and cancer, including possible relevant mechanisms and a comparison of different anthropometric measures. Finally, we examine the pathway of sex steroids in detail.

2.1. Overweight and obesity

By the World Health Organization (2022), overweight and obesity are defined as abnormal or excessive fat accumulation that can affect health. Overweight and obesity are typically defined by determining the BMI, which can be calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). By the World Health Organization (2022), overweight is defined as BMI greater than or equal to 25 kg/m^2 and obesity as BMI greater than or equal to 30 kg/m^2 (World Health Organization, 2022).
Health concerns in relation to overweight and obesity have been described in the literature. Studies reported that an increased BMI leads to an increased risk of developing cardiovascular diseases, diabetes, musculoskeletal disorders and some cancer types e.g. endometrial-, breast-, ovarian-, prostate-, and colon cancer (World Health Organization, 2022; Singh et al., 2013). Possible underlying mechanisms for an increased risk of those diseases are the metabolic consequences of obesity, such as inflammation, insulin resistance, sex steroids and dyslipidemia (Marinou et al., 2010; Singla et al., 2010; Roberts et al., 2010).

Although BMI is a very useful measure of overweight and obesity at the population level, since the same calculation is used for both sexes and all age groups in adults, there is no distinction between lean and fat mass, indication of the distribution of the latter or differences between races (World Health Organization, 2022; De Ridder et al., 2016; Williams et al., 2015). Metabolic and cardiovascular risk factors are, according to Carr and Brunzell (2004), impacted by the regional fat distribution.
Adipose tissue can be divided into two main types: subcutaneous adipose tissue, adipose tissue found between the skin and muscles, and visceral adipose tissue, which is adipose tissue in the main cavities of the body (Calle and Kaaks, 2004). In people with increased visceral fat accumulation abnormal metabolic features, such as hypertriglyceridemia, hyperinsulinism and insulin resistance have been described (Carr and Brunzell, 2004). Therefore, it is important to obtain information about fat distribution, by using other anthropometric measurements, e.g., waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) (De Ridder et al., 2016).

More than ever, overweight and obesity represent a global health concern. World Health Organization (2022) stated that since 1975 worldwide obesity has almost tripled. Data from 2016 showed that more than 1.9 billion adults (>18 years) were overweight, and 650 million of these adults were obese. These findings illustrate that 39% of the population aged 18 years or older are overweight and 13% are obese. Data on the prevalence of overweight and obesity also exists for children and adolescence (World Health Organization, 2022). In the population of children aged 5 years or younger, 39 million children were estimated to be overweight or obese in 2020. In the population of children and adolescents aged 5-19, more than 340 million were overweight or obese in 2016 (World Health Organization, 2022). Given the high prevalence of overweight and obesity, understanding the relationship between these conditions and other health outcomes, and reducing the number of overweight and obese individuals, is an urgent public health concern (World Health Organization, 2022).

2.2. Obesity/overweight and cancer risk

As described in section 2.1, obesity and overweight are associated with a higher risk of various cancer types. In this section, we examine only the associations between body fatness and the cancers of interest to our review: endometrial, ovarian, and breast cancer.

2.2.1. Endometrial cancer

There is convincing evidence that body fatness increases the risk for endometrial cancer according to research conducted by the World Cancer Research Fund (World Cancer Research Fund/American Institute for Cancer Research, 2018c), an international body which provides consensus statements on lifestyle-related factors and cancer risk formed through systematic reviews, meta-analysis and expert review panels. Analysis of individual anthropometric measures showed that people in the highest BMI category had an increased risk for endometrial cancer compared to the lowest category (World Cancer Research Fund/American Institute for Cancer Research, 2018c). Also, it was found that per 5 BMI units, the risk for endometrial cancer increased by 50% (relative risk of 1.50 (95% confidence interval (CI): 1.42-1.59)). The increased risk was found in pre- (relative risk of 1.41 (1.37-1.45)) and postmenopausal women (relative risk of 1.54 (1.39-1.71)). Furthermore, the authors also reported evidence for a positive association between endometrial cancer risk and WC and WHR. The endometrial cancer risk increased by 13% (relative risk of 1.13 (1.08-1.18)) for very 5 cm of WC, with adjustment for BMI it increased 12% (relative risk of 1.12 (1.05-1.20)) suggesting a potential independent effect of abdominal obesity. For every 0.1 unit of WHR the risk increased by 21% (relative risk of 1.21 (1.13-1.29)), with adjustment for BMI the risk was 7% (relative risk of 1.07 (0.97-1.17)) (World Cancer Research Fund/American Institute for Cancer Research, 2018c; Norat et al., 2012). Overall, World Cancer Research Fund/American Institute for Cancer Research (2018c) concluded that evidence for an association with endometrial cancer risk for overall body fatness (BMI) exists and the evidence for WCR and WHR was less robust compared to BMI. In a systematic review, De Ridder et al. (2016) investigated if the association for cancer risk is the same for whole body

(BMI) or abdominal adiposity (WC and WHR). The results are in line with the ones of World Cancer Research Fund/American Institute for Cancer Research (2018c) and show that whole body and abdominal adiposity are both associated to endometrial cancer risk in postmenopausal women. De Ridder et al. (2016) report no association between BMI or WHR and endometrial cancer risk in premenopausal women, however, only one study was investigated.

2.2.2. Ovarian cancer

For ovarian cancer, World Cancer Research Fund/American Institute for Cancer Research (2018d) concludes that there is probable evidence that body fatness increase the risk of ovarian cancer and is therefore a cause of this disease. World Cancer Research Fund/American Institute for Cancer Research (2018d) reports that for BMI, studies found significant positive, non-significant positive and non-significant negative association with ovarian cancer risk. A dose-response meta analysis showed that per 5 BMI units, the risk for ovarian cancer increased by 6% (relative risk of 1.06 (1.02-1.11)). The dose-response meta-analysis for WC showed a positive association, however this was not significant, and only 2 studies were included. For WHR, no association with ovarian cancer were identified (World Cancer Research Fund/American Institute for Cancer Research, 2018d; Norat et al., 2013). Overall, World Cancer Research Fund/American Institute for Cancer Research (2018d) concluded that evidence for an association with ovarian cancer risk for overall body fatness (BMI) exists, the evidence for WCR and WHR was inconsistent. The findings for ovarian cancer risk of the review by De Ridder et al. (2016) indicate a stronger association with whole body adiposity than abdominal adiposity, however, only one study was identified, and thus this association remains unclear. Differences in the association between higher BMI and greater risk for ovarian cancer have been found for tumour types, as reviewed by World Cancer Research Fund/American Institute for Cancer Research (2018d). An association was found for borderline serous tumours with an odds ratio of 1.24 (1.18-1.30), 1.17 (1.11-1.23) for invasive endometrioid tumours and 1.19 (1.06-1.130) for invasive mucinous tumours, but not for serous invasive cancer overall (Olsen et al., 2013; World Cancer Research Fund/American Institute for Cancer Research, 2018d). The association was higher for borderline serous than fully malignant serous tumours (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012; World Cancer Research Fund/American Institute for Cancer Research, 2018d).

2.2.3. Breast cancer

For breast cancer, possible associations with body fatness are investigated separately for pre- and postmenopausal breast cancer by World Cancer Research Fund/American Institute for Cancer Research (2018a). In premenopausal women, strong evidence exists that higher body fatness decreases the risk for premenopausal cancer. For women aged 18-30 years, the same association can be observed. The results of the dose-response meta-analysis indicate a decrease of premenopausal cancer risk of 18% (relative risk of 0.82 (0.76-0.89)) per 5 kg/m^2 in young adults (18-30 years) and a decrease of 7% (relative risk of 0.93 (0.90-0.97)) per 5 kg/m^2 in premenopausal women. Significant positive associations between WC or WHR and premenopausal breast cancer were found only after adjusting for BMI (World Cancer Research Fund/American Institute for Cancer Research, 2018a; Norat et al., 2017). Overall, World Cancer Research Fund/American

Institute for Cancer Research (2018a) concluded that higher body fatness (BMI, WC and WHR) in premenopausal women had a protective effect for premenopausal breast cancer. However, the authors also note that the increased risk of postmenopausal breast cancer due to higher body fatness outweighs the decreased risk of pre-menopausal breast cancer.

Strong evidence exists that higher body fatness throughout adulthood increases the risk for postmenopausal cancer, and higher body fatness between the age of 18-30 decrease the risk (World Cancer Research Fund/American Institute for Cancer Research, 2018a). The results of the dose-response meta-analysis for postmenopausal cancer indicate a decrease in cancer risk of 18% (relative risk of 0.82 (0.76-0.88)) per 5 kg/m^2 in young adults (18-30 years) and an increase in cancer risk of 12% (relative risk of 1.12 (1.09-1.15)) per 5 kg/m^2 in adults (World Cancer Research Fund/American Institute for Cancer Research, 2018a; Norat et al., 2017). For the association with postmenopausal breast cancer, heterogeneity can be observed for tumor hormone receptor status and use of exogenous hormones, as reviewed by Fortner et al. (2016). Significant positive associations were also found between WC or WHR and postmenopausal breast cancer in adults (World Cancer Research Fund/American Institute for Cancer Research, 2018a; Norat et al., 2017). Overall, World Cancer Research Fund/American Institute for Cancer Research (2018a) concluded that higher body fatness (BMI, WC and WHR) throughout adulthood was significantly associated with an increased risk and is therefore a convincing cause for postmenopausal breast cancer. The results of De Ridder et al. (2016) are in line with the ones of World Cancer Research Fund/American Institute for Cancer Research (2018a) and show that whole body and abdominal adiposity are both associated with breast cancer risk in postmenopausal women.

2.2.4. Weight loss and cancer risk

Beyond the associations with higher levels of body fatness and cancer risk, it is of high importance to investigate how weight loss affects this risk. A study by Luo et al. (2017) investigated the influence of weight loss on endometrial cancer risk in postmenopausal women, adjusted for BMI. The results showed, that women with a weight loss > 5% had a significant lower risk (Hazard ratio of 0.71 (95% CI: 0.54-0.95)) for endometrial cancer, compared to women with stable weight (change < 5%). Luo et al. (2017) reported, that this association was especially strong for intentional weight loss in obese women (Hazard ratio of 0.44 (0.25-0.78)). Byers and Sedjo (2011) concluded, after reviewing three bariatric surgery studies and three dietary randomized controlled trials, that weight loss achieved through bariatric surgery lowered cancer incident (all sites) and dietary intervention lowered breast cancer incidence. The bariatric surgery studies reported a reduction of 24% and 42% in women and 78% measured in men and women, the diet intervention studies report a reduction of 4%, 9% and 24% investigated in women (Byers and Sedjo, 2011). In a systematic review, Zhang et al. (2019) reported that intentional weight loss can lower the risk of endometrial cancer. For endometrial cancer, bariatric surgery (5 studies) led to 59% lower odds (Zhang et al., 2019). The result of the study by Chlebowski et al. (2019), adjusted for BMI, indicate a significant association between weight loss in postmenopausal women and reduced risk (hazard ratio of 0.88 (0.78-0.98) of breast cancer, compared to women that report stable weight (change < 5%). No studies for weight loss and ovarian cancer risk were identified.

2.3. Biological mechanisms

Multiple systemic alterations are the result of overweight and obesity. These alterations are also believed to promote the development and progression of cancer, and thus form the link between obesity and cancer (Donohoe et al., 2011). Different mechanistic systems have been identified (Roberts et al., 2010; Harris et al., 2022):

- Sex steroids
- Adipokines (e.g., adiponectin and leptin)
- Insulin and the insulin-like growth factor–I
- Cytokines and cytokine-like proteins
- Oncometabolites (e.g., lipid peroxides, reactive oxygen species and lipopolysaccharide)
- Dietary factors (e.g., glucose, fatty acids and 27-hydroxycholesterol)

Since each of these systems is very comprehensive, we focus on a single pathway covering the sex steroid hormone metabolism in this thesis. In the further course of the research project, the insulin, insulin-like growth factor–I and inflammation mechanisms will be investigated in more detail.

2.3.1. Sex steroids

Calle and Kaaks (2004) described two ways in which obesity impacts hormone production and is subsequently associated with cancer. One pathway is, the conversion of androgens Δ4-androstenedione (Δ4A) and testosterone (T) to estrone (E1) and estradiol (E2) in the adipocytes. This conversion is catalysed by the enzymes aromatase and 17β-hydroxysteroid dehydrogenase (17β-HSD), which are produced in the adipose tissue. In individuals that are obese or overweight, there is therefore an increased conversion, which results in higher concentrations of bioavailable concentrations of testosterone and estradiol (Calle and Kaaks, 2004).
Another pathway is via hyperinsulinaemia as this, as a result of obesity, leads to increased insulin levels and decreased synthesis of SHBG (Calle and Kaaks, 2004). The decreased SHBG levels contribute to the increased concentrations of bioavailable testosterone and estradiol. Once testosterone and estradiol bind to their receptors in the target cells, cellular proliferation can be increased and apoptosis decreased (Calle and Kaaks, 2004). This mechanism is illustrated in Figure 2.1.
There is data on a possible association between higher levels of circulating sex steroids and higher risk of cancer (Hormones, Endogenous and Breast Cancer Collaborative Group, 2013; Brown and Hankinson, 2015; Hormones, Endogenous and Breast Cancer Collaborative Group, 2015; Allen et al., 2008; Ose et al., 2017; Trabert et al., 2019). This association is particularly well investigated for endometrial, ovarian and breast cancer and will be described in further detail in Section 5.

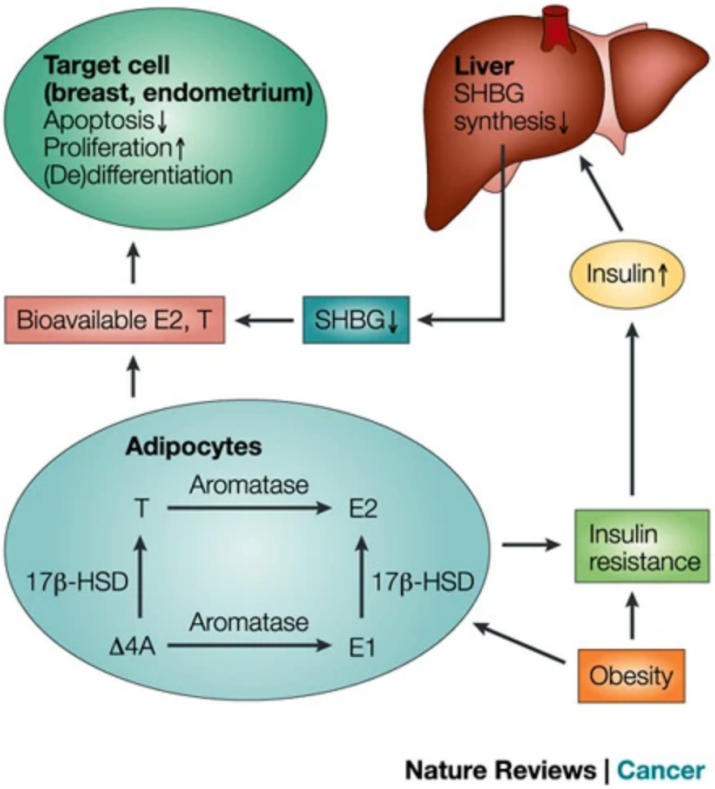


Figure 2.1.: Influence of obesity on the production of sex steroids. Oestrone (E1), Oestradiol (E2), Testosterone (T), Sex hormone-binding globulin (SHBG), 17β-hydroxysteroid dehydrogenase (17β-HSD), Δ4-androstenedione (Δ4A). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature Reviews Cancer, (Calle and Kaaks, 2004).

3. Methods

This thesis is conducted as part of an ongoing large systematic literature review project. Therefore, not all the steps mentioned in the method section were conducted by myself.

3.1. Literature search

The literature search for this review was divided into several phases. First, we identified the studies that were relevant to our systematic review and met the criteria for inclusion (the inclusion and exclusion criteria will be specified shortly). For this search, we used the databases *Pubmed* and *Web of Science*. To obtain only relevant studies, we defined specific search terms that are used as an additional filter, as shown in Table 3.1. With these search terms, we filtered for body composition synonyms and measurements, our key exposures of interest, sex steroids, our main outcome of interest, study type, study population, and languages in the title and abstract that we are interested in. The same search terms were used during the *Pubmed* and *Web of science* search. Using both platforms resulted in the identification of 24,737 records. After removing the duplicates, 7,862 records, a total of 16,875 possible relevant studies were identified.

Number	Search terms
1	body fatness[Title/Abstract] OR adiposity[Title/Abstract] OR obesity[Title/Abstract] OR obese [Title/Abstract] OR abdominal obesity[Title/Abstract] OR morbid obesity[Title/Abstract] OR metabolic obesity[Title/Abstract] OR overweight[Title/Abstract] OR over-weight [Title/Abstract] OR over weight [Title/Abstract] OR BMI[Title/Abstract] OR body mass index[Title/Abstract] OR waist-Hip ratio[Title/Abstract] OR waist to hip ratio[Title/Abstract] OR waist-height ratio[Title/Abstract] OR waist to height ratio[Title/Abstract] OR waist hip ratio*[Title/Abstract] OR intra-abdominal fat[Title/Abstract] OR adipocytes[Title/Abstract] OR adipose tissue[Title/Abstract] OR weight loss[Title/Abstract] OR weight gain[Title/Abstract] OR anthropometry[Title/Abstract] OR body composition [Title/Abstract] OR body mass [Title/Abstract] OR skinfold measurement* [Title/Abstract] OR skinfold thickness[Title/Abstract] OR bio-impedence[Title/Abstract] OR waist circumference[Title/Abstract] OR hip circumference[Title/Abstract] OR body composition[Title/Abstract] OR body constitution[Title/Abstract]

2	Estrogens[Title/Abstract] OR Estrogen[Title/Abstract] OR Oestrogens[Title/Abstract] OR Oestrogen*[Title/Abstract] OR Oestrogen*[Title/Abstract] OR Estrone[Title/Abstract] OR Oestrone[Title/Abstract] OR Estradiol[Title/Abstract] OR Oestradiol[Title/Abstract] OR Estrone[Title/Abstract] OR Oestrone[Title/Abstract] OR sex hormone*[Title/Abstract] OR sex steroid*[Title/Abstract] OR estriol[Title/Abstract] OR Oestriol [Title/Abstract] OR estrogen metabolites[Title/Abstract] OR androgens[Title/Abstract] OR androgen metabolites[Title/Abstract] OR dehydroepiandrosterone[Title/Abstract] OR androstenedione[Title/Abstract] OR androstenediol[Title/Abstract] OR androsterone[Title/Abstract] OR testosterone[Title/Abstract] OR progesterone[Title/Abstract] OR sex hormone binding globulin[Title/Abstract] OR sex hormone-binding globulin[Title/Abstract] OR estrogen receptor[Title/Abstract] OR progesterone receptor[Title/Abstract] OR hormone receptor[Title/Abstract] OR estrobolome[Title/Abstract]
3	1 AND 2
4	animal[MeSH Terms] NOT human[MeSH Terms]
5	animal[Title/Abstract]NOT human[Title/Abstract]
6	4 OR 5
7	3 NOT 6
8	Corrigendum[Title/Abstract] OR letter[Title/Abstract] OR comment[Title/Abstract] OR erratum[Title/Abstract] OR Comment in[Title/Abstract] OR Comment on[Title/Abstract] OR Erratum in[Title/Abstract] OR Erratum for[Title/Abstract] OR Expression of concern in[Title/Abstract] OR Expression of concern for[Title/Abstract]
9	7 NOT 8
10	narrative review*[Title/Abstract] OR systematic review*[Title/Abstract] OR scoping review*[Title/Abstract] OR review*[Title/Abstract] OR meta-analys*[Title/Abstract] OR meta analys*[Title/Abstract] OR metaanalys*[Title/Abstract]
11	9 AND 10
12	book[Title/Abstract] OR books[Title/Abstract] OR pmcbook[Title/Abstract] OR book chapters[Title/Abstract] OR pmcbooktitle[Title/Abstract] OR pmcbookchapter[Title/Abstract] OR chapter[Title/Abstract] OR chapters[Title/Abstract] OR chapter*[Title/Abstract]
13	11 NOT 12
14	11 with language filter: English
15	11 with language filter: German
16	11 with language filter: French
17	11 with language filter: Dutch
18	14 OR 15 OR 16 OR 17
19	13 with age filter: 19+ years

Table 3.1.: Terms for literature search

3.2. Screening

During the second phase of the literature search, the title, and abstracts of the 16,875 studies were screened using the online screening tool named Covidence. Each study was screened by 2 reviewers. The criteria for inclusion or exclusion of a study are provided in the following paragraph. A total of 908 studies out of the 16,875 studies were selected for full text review and therefore forwarded to the next screening phase.

Inclusion criteria

- Articles **must** report some measures of association between body fatness and sex steroid markers in title/abstract
- Articles **must** be in women and of any of the following design:
  - Randomized controlled trial
  - Group randomized controlled trial (Community trial)
  - Prospective cohort study
  - Nested case-control study
  - Case-cohort study
  - Population based case-control study
  - Clinical case series
- Articles **must** include one of the following outcomes:
  - Estrogen, Estrone, Estradiol, sex hormone, sex steroid, estriol, androgen, dehydroepiandrosterone (DHEA), androsterone, testosterone, progesterone, SHBG, estrogen receptor, progesterone receptor, Beta-17 estradiol fatty acid, 16-alpha-hydroxyestrone (16-alpha OHE-1), 2-Hydroxyestrone (2-OHE-1), 2-Hydroxyestrone to 16 ahydroxystrone ratio (ratio 2OHE1 to 16OHE1), 17-alpha-hydroxyprogesterone (hydroxyprogesterone), Dihydroesterone (DHT), hydroxysteroid dehydrogenase 1 and 2, aromatase (CYP19A1), Aromatase activity, Aromatase expression, Aromatase P11, Aromatase P1.3, P11 derived aromatase mRNA, P1.3 derived aromatase mRNA, PR level, Estrone-fatty acid ester
- Articles **must** include relevant exposures (Body fatness) in relation to outcome
  - Direct (measures of adiposity (i.e. measurements of whole-body composition assessed by dual-energy X-ray absorptiometry, and abdominal subcutaneous and visceral adipose tissue (VAT) volume, by magnetic resonance imaging, adipocyte size), or indirect (BMI, WHR, Waist circumference, skinfold thickness)

- Associations: Include when the association is presented the other way around, i.e. WHR is different between sex steroid groups. Include if there is no association but averages of sex steroid per subgroups of body fatness are reported
- 18 years old or older
- Women only, or men and women with stratified analysis for sex differences
- Published in English
- Published in peer-reviewed journal
- In case of exogenous hormone intake (hormone replacement therapy (HRT) or oral contraceptives (OC)), the analysis must be stratified by user/none user for estrogen and progesterone association with adiposity
- In premenopausal women, the association adiposity with estradiol or progesterone should be adjusted for menstrual cycle, or blood sample should have been taken at a specific time of the menstrual cycle. But, studies were included also if the menopausal status was not reported.

Exclusion criteria

- Articles are excluded if:
  - They are out of research topic
  - They are not reporting measure of relationship
  - A reverse causation is clearly evident in the abstract
  - They are not in English
  - The study population restricted to men, or sex differences not evaluated
  - The study population is younger than 18 years old
  - Women are taking HRT or OC, but the analysis is not stratified by user/none user
  - Hormone level (also estradiol/progesterone) is not adjusted for menstrual cycle (premenopausal women)
- Articles are excluded if they are one of the following study design:
  - Systematic reviews and/or pooled analysis (were used to inform and to ensure we were not duplicating existing research)
  - Animal and cell line studies
  - Studies on body fatness and cancer without a mechanistic component
  - Study on cancer survival
- Articles are excluded if the only outcome is one of the following:

  - cortisol, cortisone
  - Luteinizing hormone (LH)
  - Exogenous hormone
  - Aldosterone

- Exposure excluded:
  - Diet or physical activity are not surrogate for body fatness (include if the paper reports weight change related to SS).
  - Surrogate for obesity are not included: Non-alcoholic fatty liver disease (NAFLD) or collateral disease to obesity
  - Adiponectin, leptin, adipocyte fatty acid-binding protein (express in adipocyte) are not established maker for body fatness.

- Articles are excluded if the population includes the following Preconditions:
  - Transgender
  - In vitro fertilization pregnancies
  - Pregnancy: except if sex steroids concentrations and adiposity are reported before pregnancy.
  - tuberculosis
  - Anorexia nervosa
  - Fibromyalgia
  - NAFLD
  - Infertility
  - Polycystic ovary syndrome (PCOS)
  - Diabetes
  - Irregular menstrual cycle

3.3. Full text review

The third and final phase of the literature search was full-text screening. Studies reporting only an association between circulating sex steroids and BMI were excluded, since systematic reviews are already published on the topic. Restriction to healthy women was also done at that stage. Each article was reviewed by one reviewer only in the full-text screening phase. Of the 908 studies reviewed, 174 were deemed suitable and therefore included in the review. A total of 24 studies on Tissue markers, 25 excreted markers (saliva, urine, breast ductal lavage), 41 intervention studies, 57 observational studies with direct measure of adiposity (radiology image), and an additional 27 on mammographic density and sex steroids. Only studies reporting weight change between 2

time points, at least 3 months apart, were investigated in this thesis: 41 intervention studies, one cross-sectional, and one cohort study.

Refined inclusion/exclusion criteria

- The intervention period should be at least 3 months, and the change in body fatness should be significant
- Exclude if the intervention period is less than 3 months
- Exclude if the study reports no significant change in body fatness

3.4. Data extraction

3.4.1. General extraction

To begin the meta-analysis of the identified studies, the relevant data were extracted in *EPIinfo* (the database for extraction created for the project). The extracted data included information about the study (e.g. Author and Year), the population (e.g. age), the intervention (e.g. intervention type and duration), the type of body fatness and sex steroids assessed in the study and with the according values and the measure of association between them. In addition, the dataset includes an assessment of the risk of bias for each study.

3.5. Data management and cleaning

Once the data were extracted, we proceeded with cleaning and preparing it for the analysis. The studies were, again, reviewed for inclusion or exclusion, any missing data were extracted, and additional information needed for the analysis was extracted or calculated. The calculated data included, for example, the change of body fatness between the baseline and follow-up time point, harmonizing hormone values to the same unit or converting Interquartile range to standard deviation.

For data analysis, we used R (R Core Team, 2021). First, the dataset had to be cleaned and reshaped, which we achieved by reorganizing the rows and columns of each study and removing duplicate information. Furthermore, the relevant studies were evaluated to determine whether they should be included in the meta-analysis or described in narrative form, where the data across studies were too heterogeneous and therefore not amenable to meta-analyse. Narrative form was used if, for example, no measure of variance (e.g. standard deviation (SD)) was mentioned, only the amount of change of a sex steroid was reported but no baseline/follow-up value, or a sex steroid type was only investigated by one study.

3.6. Data analysis

All steps of the analysis were performed using the programming language R (R Core Team, 2021). To obtain an overview of the data, we conducted a frequency analysis of the type of measured body fat, type of sex steroid and the duration of the intervention period. Visualizations were done using bar charts. We show the respective results in Figures 4.1, 4.2 and 4.3. Furthermore, we also investigated the baseline values of the body composition measures and sex steroids (Figures 4.4,4.5 and 4.6). As those values are presented in different units, we harmonized the baseline units for a better interpretation.

The main part of the analysis focused on investigating, if a change in body fatness achieved by a given intervention type results in a change in concentration of the circulating sex steroid. The packages used to perform the analysis, and also the graphical demonstration of the result, were `meta` (Balduzzi et al., 2019) and `dmetar` (Harrer et al., 2019). An advantage of the `meta` packages is, that the standardized mean difference (SMD) between baseline and follow-up time-point is used for the analysis, instead of the absolute mean difference in values. This was important since the included studies measured the same sex steroids, but using various units, and this allowed us to leave the values in the original units for the meta-analysis. Therefore, before starting the analysis, it was required to calculate the SMD and the standard error (SE)) for each study. For this, we used the *within-group (standardized) Mean Difference* as the same population was measured at two different time points (Harrer et al., 2021).

The data was meta-analysed using the `metagen` function with the random effects model. The study samples included in the systematic review are not homogeneous, and the measurements of the outcomes and also the type and duration of the interventions differed, which will lead to variance in the effect size. Therefore, we chose to use the random effects model because it presumes a distribution of true effect sizes rather than a single true effect size. The results of the analysis provide information on which and how many studies were included, as well as the corresponding effect sizes and 95% CI. The main results included, are the pooled effect size with its 95% CI and the significance of the effect size. Furthermore, information on the between-study heterogeneity is provided as τ^2 , I^2 and the p value. τ^2 is defined as the variance of the distribution of the effect sizes and I^2 is quantified as the percentage of variability, not caused by sampling error, in the effect sizes (Harrer et al., 2021).

To visualize these findings, we generated forest plots for the individual sex steroids using the `forest.meta function` which are presented in section 4.2. These plots also contain information on the number of participants, the duration of the intervention and the percent change in body composition between baseline and follow-up. Additionally, we stratified the analysis by menopausal status for estradiol, free estradiol and estrone, and by the type of body composition measurement.
To further investigate the data, the results and large heterogeneities, outlier analyses were performed. With outlier analysis, it is possible to identify studies with an extreme effect size, which results in a high between-study heterogeneity and a distorted pooled effect estimate. For this,

we used the `find.outliers` function of the `dmetar` package (Harrer et al., 2019). Harrer et al. (2019) define an outlier as a study, where the CI is not overlapping with the pooled effect CI. Therefore, this package searches for studies where the upper bound of the 95% CI is lower than the lower bound of the CI of the pooled effect or the lower bound of the 95% CI is higher than the upper bound of the pooled effect CI. After the identification of an outlier, the package removes the identified outlying studies and reruns the calculation of the effect size and heterogeneity (Harrer et al., 2021). Furthermore, we reviewed the full text of outlying studies to identify possible explanations of the extreme effect sizes observed.

3.7. Risk of bias

For our meta-analysis, it is crucial to analyse the results and data of the individual studies while also evaluating possible bias so that the overall interpretation of the summary of associations can be made in the context of the strengths and weaknesses of the contributing studies. Without knowledge of the quality of the study, it is only to a limited extent possible to interpret and classify the findings correctly. Therefore, a Risk of Bias (RoB) assessment was performed on all included studies. However, since different study designs with different requirements were examined, the components of the ROB-assessment differed slightly. It is important to note that in the ROB-assessment of all study designs, the answer option 'yes' can represent both high and low study quality, the same applies for no.

For the non-randomized intervention studies, we used the ROBINS-I tool (Sterne et al., 2016). This instrument contains a range of questions within 7 domains that covers areas in which bias are most likely to occur. This includes confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and Bias in selection of the reported result (Sterne et al., 2016). The questions included in each domain were answered with:

- Yes
- Partially Yes
- Partially No
- No
- Not Applicable
- No Information

The summary question at the end of each domain, which focused on the risk, were answered with:

- Low
- Moderate
- Serious

- Critical
- No information

The overall judgment of the studies was made according to the recommendations of the ROBINS-I tool, which are as follows:

- A study is at **low** risk of bias if all domains are judged to be at low risk
- A study is at **moderate** risk if all domains are low or moderate risk
- A study is at **serious** risk if at least one domain is at serious, but not at critical risk
- A study is at **critical** risk if at least one domain is at critical risk
- No information

(Sterne et al., 2016)

Our ROB-assessment for the randomized trials, cross-sectional and cohort studies only defer by a few questions, therefore we will discuss them together in this section. All assessments primarily contained questions from the NIH quality assessment tool (National Heart, Lung, and Blood Institute, 2020), however, we complemented them with questions from the ROBINS-E (Risk Of Bias In Non-randomized Studies of Exposures) (University of Bristol, 2020) and the Quality Assessment Tool for Quantitative Studies by the Effective Public Health Practice Project (Evans et al., 2015). A total of 15-19 questions were surveyed with the option of answering:

- Yes
- No
- Not Applicable
- No Information

All three questionnaires include questions on the: objectives, hypothesis, description of the population, participation rate, selection of participants, sample size, exposure prior to outcome, follow-up, measure of the outcome, blinding, confounding, analysis method, missing data and bias in selection of reported result. Additionally, the questionnaire of the randomized trials included questions on randomization, loss in follow-up and compliance. The questionnaire of the cohort studies included additional questions on loss in follow-up, compliance, observer bias, comparability of measurements across study participants and exposure in category. And the questionnaire of the cross-sectional studies included questions on observer bias, comparability of measurements across study participants and exposure in category. The options for the overall judgment are as follows:

- A study is at **minimal** risk of Bias
- A study is at **medium** risk of Bias
- A study is at **maximal** risk of Bias

4. Results

In this chapter, we present the results of our analysis. First, we start with describing the data included in the data set. Then, we focus on the meta-analysis and the graphical representation. For this, we conduct separate analysis for the surgical interventions and the lifestyle interventions, namely diet and/or exercise interventions.

4.1. Overview of the data

4.1.1. Dataset

The data set includes a total of 43 studies, 14 of those were surgical intervention, 29 lifestyle intervention studies and 2 reported weight change but no intervention (as shown in summary tables A.1 and A.2). Table A.1 contains information for the included studies such as the author name, year, menopausal status, study design, intervention type and duration, a description of the sample and sample size. Table A.2 contains information on author name, body fatness measure, outcome measure, comments (e.g., if described in a narrative way), summary findings and ROB assessment.
Diet, exercise, or diet+exercise interventions were grouped together as lifestyle interventions, as the initial average weight and the amount of weight loss were similar. In our data, 17 studies included a pre- and 18 a postmenopausal population, 4 studies included pre and postmenopausal women and 3 studies did no report menopausal status. 15 studies are described in a narrative way, 2 studies include one sex steroid that had to be analysed in a narrative way.

4.1.2. Baseline qualitative analysis of body fatness and sex steroids

Body composition

As displayed in Figure 4.1, the surgical interventions (n=14 studies) mainly used weight and BMI to classify body composition. In total, 9 studies calculated BMI and 8 measured weight. Fat mass (2 studies), hip- (1 study) and waist circumference (1 study) were assessed less frequently. A similar trend can be seen in Figure 4.1 in the lifestyle interventions (n=27 studies). Here, 11 studies measured weight and 8 studies calculated BMI. In the lifestyle interventions, those measurements were accompanied by percent body fat (9 studies), fat mass (10 studies). Other measures that were used by more than one study included VAT (4 studies), Waist circumference (4 studies), WHR (2 studies), Hip circumference(2 studies).

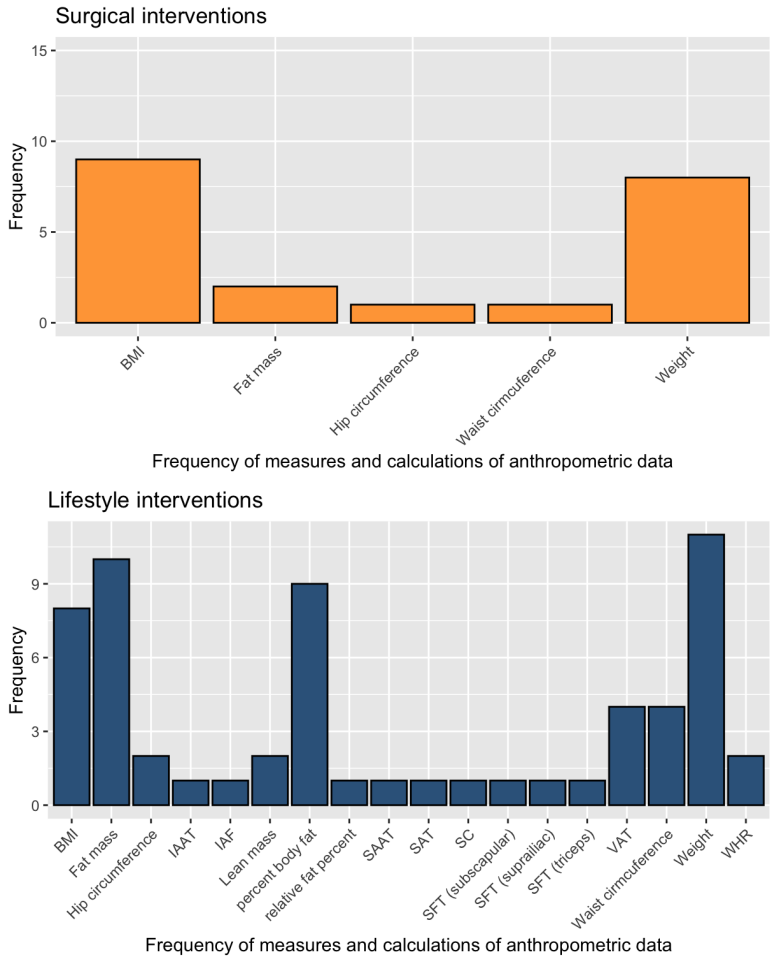


Figure 4.1.: Type and frequency of used anthropometric data. Body mass index (BMI), intra-abdominal adipose tissue (IAAT), intra-abdominal fat (IAF), subcutaneous abdominal adipose tissue (SAAT), subcutaneous adipose tissue (SAT), abdominal fat area (SC), skinfold thickness (SFT), visceral adipose tissue (VAT), waist hip ratio(WHR)

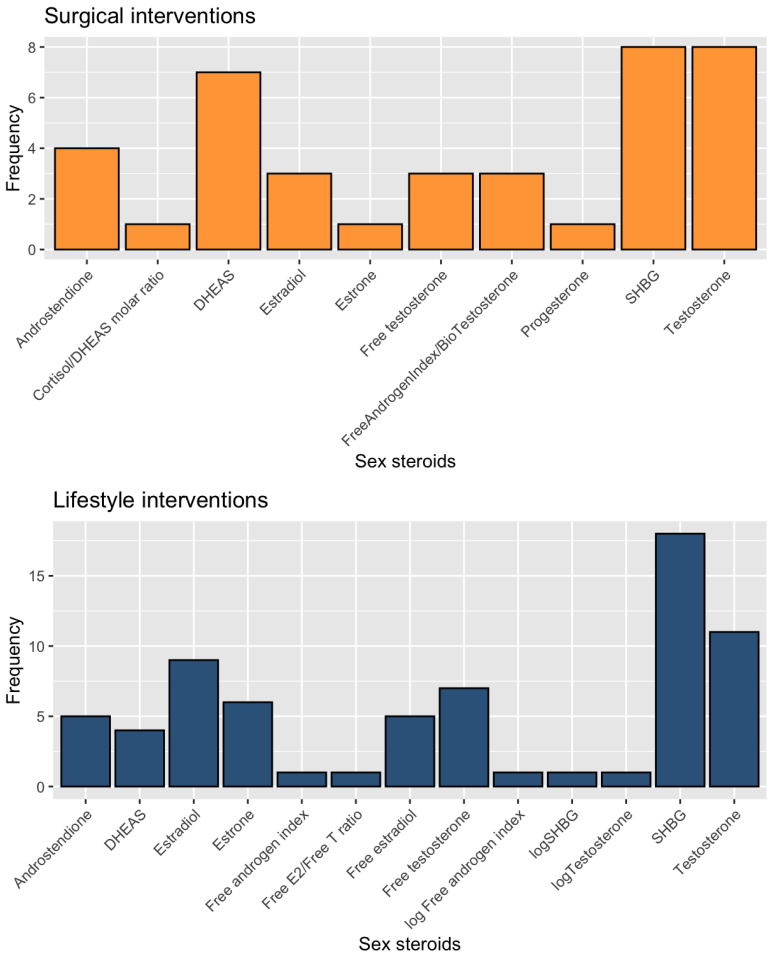


Figure 4.2.: Type and frequency of measured sex steroids. Dehydroepiandrosterone-sulfat (DHEAS), Sex hormone-binding globulin (SHBG), Estradiol (E2)

Sex steroids

In Figure 4.2, we show the frequency of the measured sex steroids in surgical and lifestyle interventions. The most evaluated sex steroids by the surgical intervention studies are SHBG (8 studies), testosterone (8 studies) and dehydroepiandrosterone-sulfate (DHEAS) (7 studies). Androstenedione (4 studies), estradiol (3 studies), free testosterone (3 studies) and progesterone (1 study) were measured less frequently. The sex steroids measured primarily by the lifestyle interventions are SHBG (18 studies), testosterone (11 studies) and estradiol (9 studies). Free testosterone (7 studies), estrone (6 studies), free estradiol (5 studies), androstenedione (5 studies), DHEAS (4 studies) and free androgen index (1 study) were assessed less often.

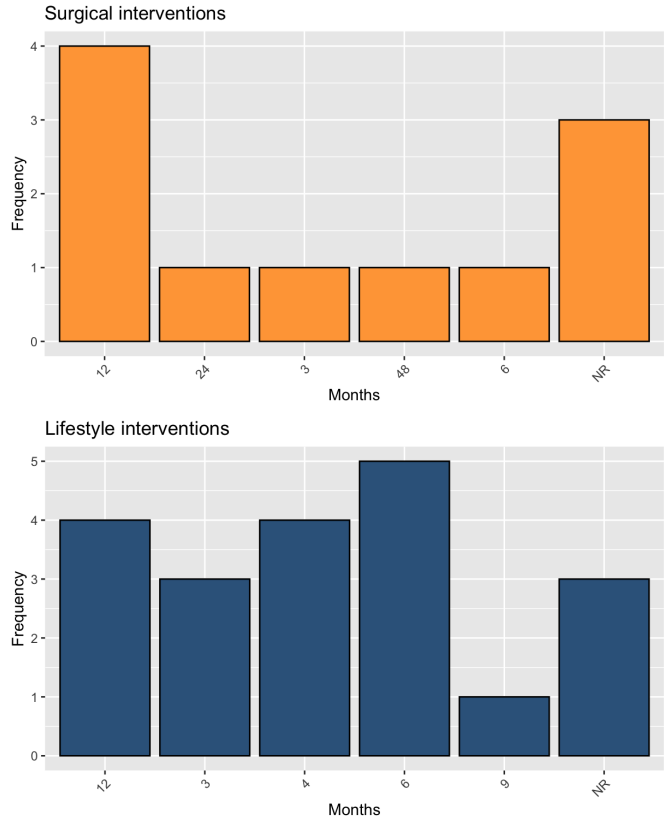


Figure 4.3.: Duration of intervention. Not reported (NR) in Surgical intervention = 8-26 months, 8-31 months and a mean of 7.9 months until stable weight loss; NR in lifestyle intervention = 3-4, 4-6 and an average of 13,5 months.

Duration of the intervention

The durations of the surgical and lifestyle interventions, which are shown in Figure 4.3 were also investigated. Only a few of the surgical intervention used the same duration. A 12-month intervention duration was used by 4 studies, the other durations were all only used by one study, ranging from 3-48 months. The mean intervention duration for surgical studies was 16 months, with a range of 3 to 48 months. For lifestyle interventions, the intervention period is much more uniform. Here, too, different time spans were selected, but the range is smaller. The most frequently used durations were 12 (4 studies), 6 (5 studies), 4 (4 studies) and 3 months (3 studies). The mean intervention duration for lifestyle studies was 6.7 months, with a range of 3 to 13.5 months.

4.1.3. Baseline quantitative analysis of body fatness and sex steroids

Body composition

In Figure 4.4 we show the baseline anthropometric data of the surgical interventions and Figure 4.5 for the lifestyle interventions. The mean baseline BMIs of the surgical intervention studies were between 43.9 and 56.7 kg/m^2, compared to the lifestyle interventions with mean baseline BMIs between 25.0 and 36.1 kg/m^2. A similar pattern was observed for baseline weight and fat mass. The mean weight of the participants in the surgical intervention studies is between 110.40 and 148.0 kg, and of the lifestyle interventions between 78.0 and 105.2 kg and one study with a mean weight of 121.6 kg. The mean baseline fat mass was substantially higher in the surgical intervention studies (64.3 and 65.9 kg) in comparison to the lifestyle intervention studies (14.3 to 47.2 kg). However, only two surgical intervention studies compared to 13 lifestyle studies measured fat mass.

Sex steroids

Figure 4.6 displays the baseline sex steroid values of the surgical and lifestyle interventions. This plot shows that the values of the studies included in each sex steroid subgroup are rather similar and only a few studies differ from those. For DHEAS the combined average is 1.35 µg/ml 95%CI (0.95;1.74). The combined average of SHBG is 55.42 nmol/L 95%CI (35.33;75.51). Kim and Kim (2012) differs heavily from the other studies, with a mean of 358.20 nmol/L. For testosterone, the combined average is 34.05 ng/dL 95%CI (29.38;38.72). The combined average for free testosterone is 113.50 pg/ml 95%CI (-120.85;347.84). However, Kovacikova et al. (2008) differs with a mean of 1526.40 pg/ml from the other studies. For Estradiol, the combined average is 35.53 pg/mL 95%CI (17.55;53.51), for free estradiol 0.34 pg/mL 95%(0.00;0.68) and for estrone 3.73 ng/dL 95%CI (2.63;4.83). For Androstenedione, the combined average is 128.49 ng/mL 95%CI (-43.67;300.65). This high average is caused by the Di Carlo et al. (1999) and, Harvie et al. (2011) as their mean values differ heavily.

4.2. Analysis

4.2.1. DHEAS

Surgical interventions

In Figure 4.7 the SMD between baseline and follow-up of DHEAS for each study, that included a surgical intervention, are shown. Seven studies were included in the meta-analysis for BMI change. The overall SMD is 0.26 95%CI (-0.79; 1.30). Nearly all studies show a decrease in BMI and a decrease in DHEAS except for Di Carlo et al. (1999), who reports a slightly positive and Savastano et al. (2005) a strongly positive SMD. However, only Beiglböck et al. (2020) and Savastano et al. (2005) observed statistically significant associations. This difference results in a high heterogeneity between the individual studies (I^2 is 90 % and τ^2 = 1.13).
Since a high between study heterogeneity was observed, we conducted an outlier analysis to

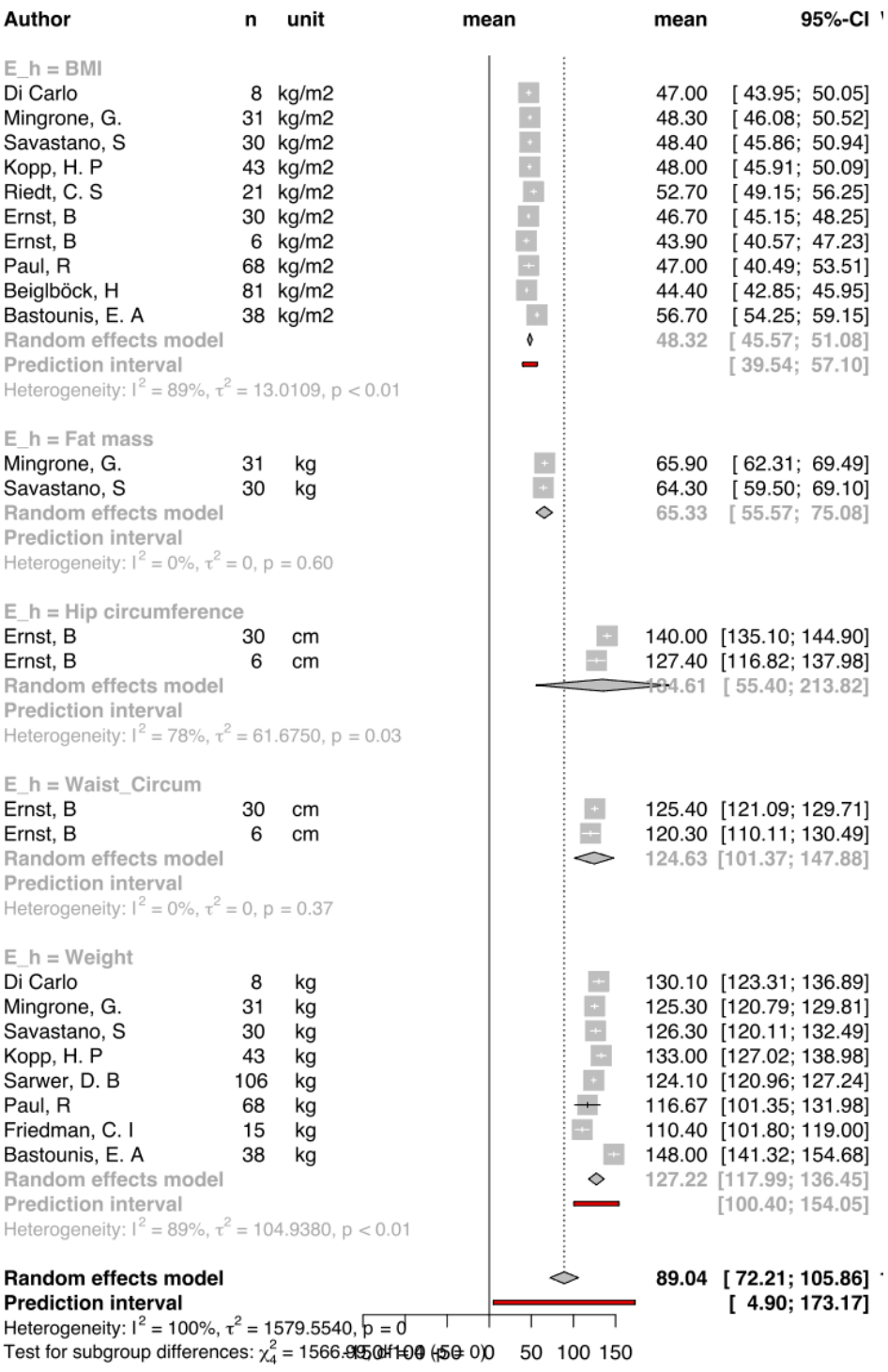
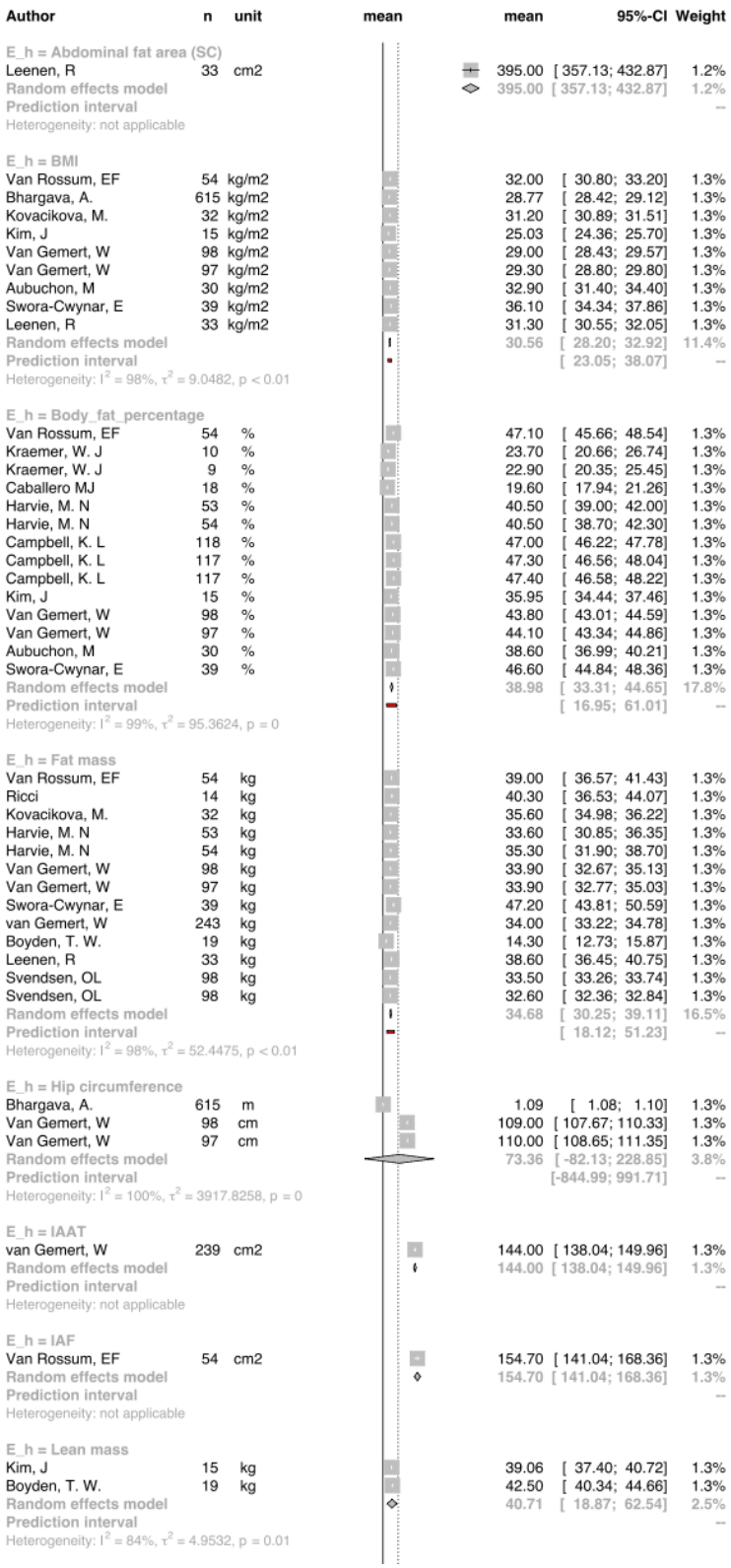


Figure 4.4.: Baseline anthropometric data of surgical interventions.


Author n unit mean mean 95%-CI Weight
E_h = Abdominal fat area (SC)
Leenen, R 33 cm2 395.00 [357.13; 432.87] 1.2%
Random effects model 395.00 [357.13; 432.87] 1.2%
Prediction interval --
Heterogeneity: not applicable
E_h = BMI
Van Rossum, EF 54 kg/m2 32.00 [30.80; 33.20] 1.3%
Bhargava, A. 615 kg/m2 28.77 [28.42; 29.12] 1.3%
Kovacikova, M. 32 kg/m2 31.20 [30.89; 31.51] 1.3%
Kim, J 15 kg/m2 25.03 [24.36; 25.70] 1.3%
Van Gemert, W 98 kg/m2 29.00 [28.43; 29.57] 1.3%
Van Gemert, W 97 kg/m2 29.30 [28.80; 29.80] 1.3%
Aubuchon, M 30 kg/m2 32.90 [31.40; 34.40] 1.3%
Swora-Cwynar, E 39 kg/m2 36.10 [34.34; 37.86] 1.3%
Leenen, R 33 kg/m2 31.30 [30.55; 32.05] 1.3%
Random effects model 30.56 [28.20; 32.92] 11.4%
Prediction interval [23.05; 38.07] --
Heterogeneity: I^2 = 98%, τ^2 = 9.0482, p < 0.01
E_h = Body_fat_percentage
Van Rossum, EF 54 % 47.10 [45.66; 48.54] 1.3%
Kraemer, W. J 10 % 23.70 [20.66; 26.74] 1.3%
Kraemer, W. J 9 % 22.90 [20.35; 25.45] 1.3%
Caballero MJ 18 % 19.60 [17.94; 21.26] 1.3%
Harvie, M. N 53 % 40.50 [39.00; 42.00] 1.3%
Harvie, M. N 54 % 40.50 [38.70; 42.30] 1.3%
Campbell, K. L 118 % 47.00 [46.22; 47.78] 1.3%
Campbell, K. L 117 % 47.30 [46.56; 48.04] 1.3%
Campbell, K. L 117 % 47.40 [46.58; 48.22] 1.3%
Kim, J 15 % 35.95 [34.44; 37.46] 1.3%
Van Gemert, W 98 % 43.80 [43.01; 44.59] 1.3%
Van Gemert, W 97 % 44.10 [43.34; 44.86] 1.3%
Aubuchon, M 30 % 38.60 [36.99; 40.21] 1.3%
Swora-Cwynar, E 39 % 46.60 [44.84; 48.36] 1.3%
Random effects model 38.98 [33.31; 44.65] 17.8%
Prediction interval [16.95; 61.01] --
Heterogeneity: I^2 = 99%, τ^2 = 95.3624, p = 0
E_h = Fat mass
Van Rossum, EF 54 kg 39.00 [36.57; 41.43] 1.3%
Ricci 14 kg 40.30 [36.53; 44.07] 1.3%
Kovacikova, M. 32 kg 35.60 [34.98; 36.22] 1.3%
Harvie, M. N 53 kg 33.60 [30.85; 36.35] 1.3%
Harvie, M. N 54 kg 35.30 [31.90; 38.70] 1.3%
Van Gemert, W 98 kg 33.90 [32.67; 35.13] 1.3%
Van Gemert, W 97 kg 33.90 [32.77; 35.03] 1.3%
Swora-Cwynar, E 39 kg 47.20 [43.81; 50.59] 1.3%
van Gemert, W 243 kg 34.00 [33.22; 34.78] 1.3%
Boyden, T. W. 19 kg 14.30 [12.73; 15.87] 1.3%
Leenen, R 33 kg 38.60 [36.45; 40.75] 1.3%
Svendsen, OL 98 kg 33.50 [33.26; 33.74] 1.3%
Svendsen, OL 98 kg 32.60 [32.36; 32.84] 1.3%
Random effects model 34.68 [30.25; 39.11] 16.5%
Prediction interval [18.12; 51.23] --
Heterogeneity: I^2 = 98%, τ^2 = 52.4475, p < 0.01
E_h = Hip circumference
Bhargava, A. 615 m 1.09 [1.08; 1.10] 1.3%
Van Gemert, W 98 cm 109.00 [107.67; 110.33] 1.3%
Van Gemert, W 97 cm 110.00 [108.65; 111.35] 1.3%
Random effects model 73.36 [-82.13; 228.85] 3.8%
Prediction interval [-844.99; 991.71] --
Heterogeneity: I^2 = 100%, τ^2 = 3917.8258, p = 0
E_h = IAAT
van Gemert, W 239 cm2 144.00 [138.04; 149.96] 1.3%
Random effects model 144.00 [138.04; 149.96] 1.3%
Prediction interval --
Heterogeneity: not applicable
E_h = IAF
Van Rossum, EF 54 cm2 154.70 [141.04; 168.36] 1.3%
Random effects model 154.70 [141.04; 168.36] 1.3%
Prediction interval --
Heterogeneity: not applicable
E_h = Lean mass
Kim, J 15 kg 39.06 [37.40; 40.72] 1.3%
Boyden, T. W. 19 kg 42.50 [40.34; 44.66] 1.3%
Random effects model 40.71 [18.87; 62.54] 2.5%
Prediction interval --
Heterogeneity: I^2 = 84%, τ^2 = 4.9532, p = 0.01

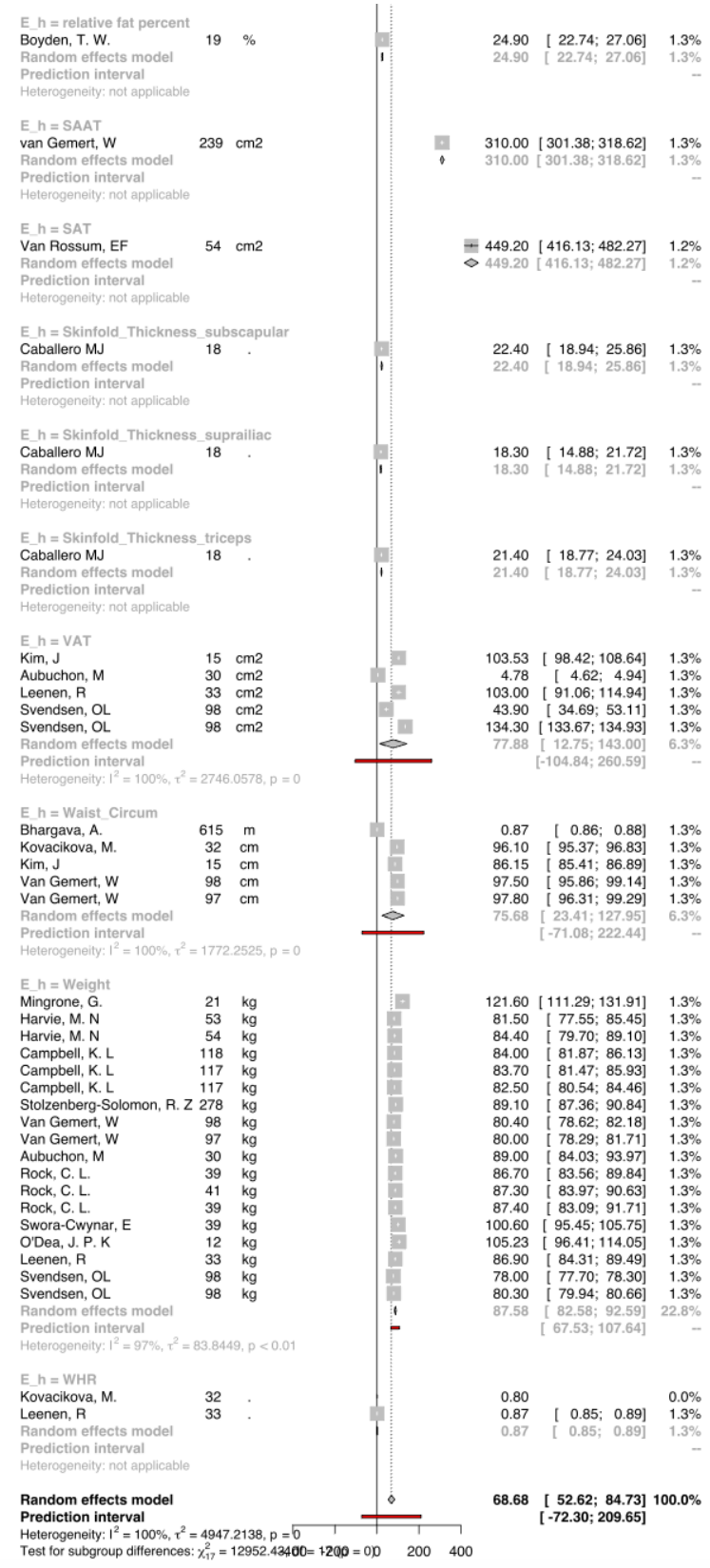
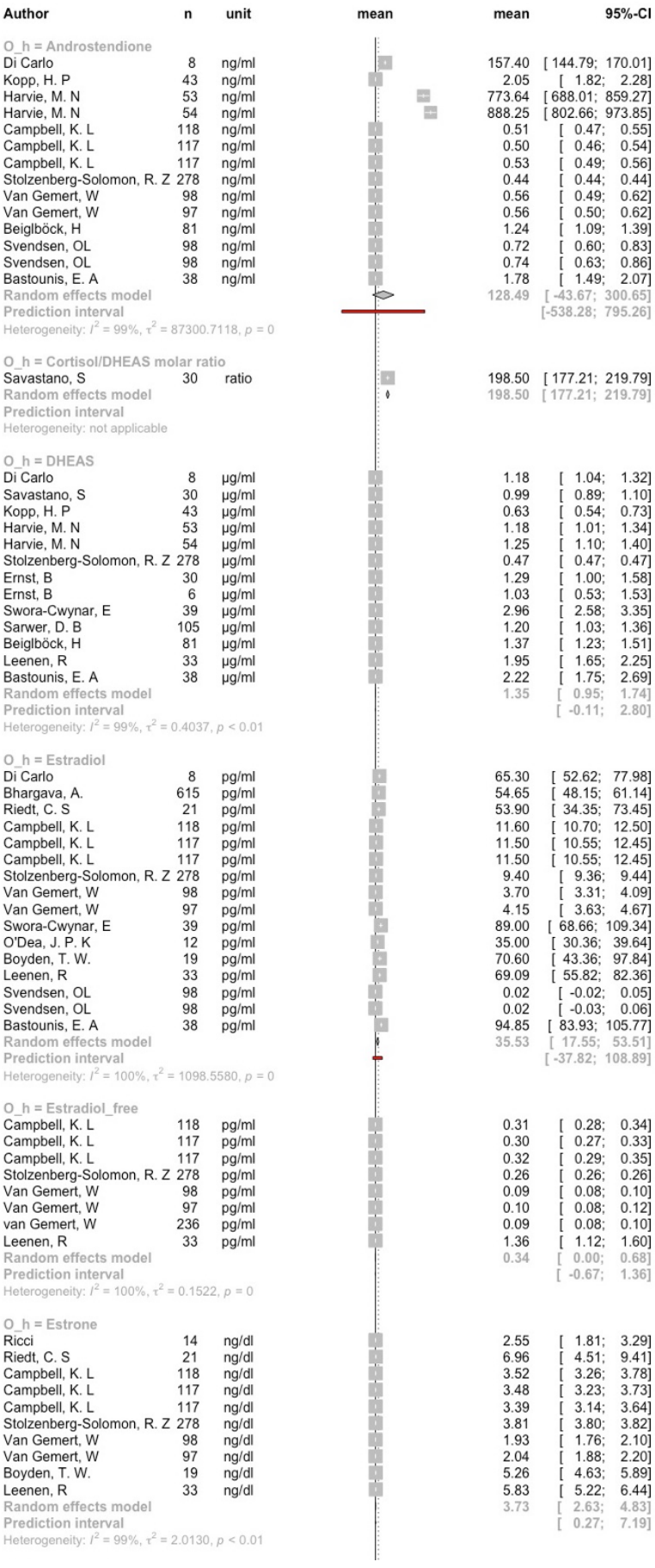
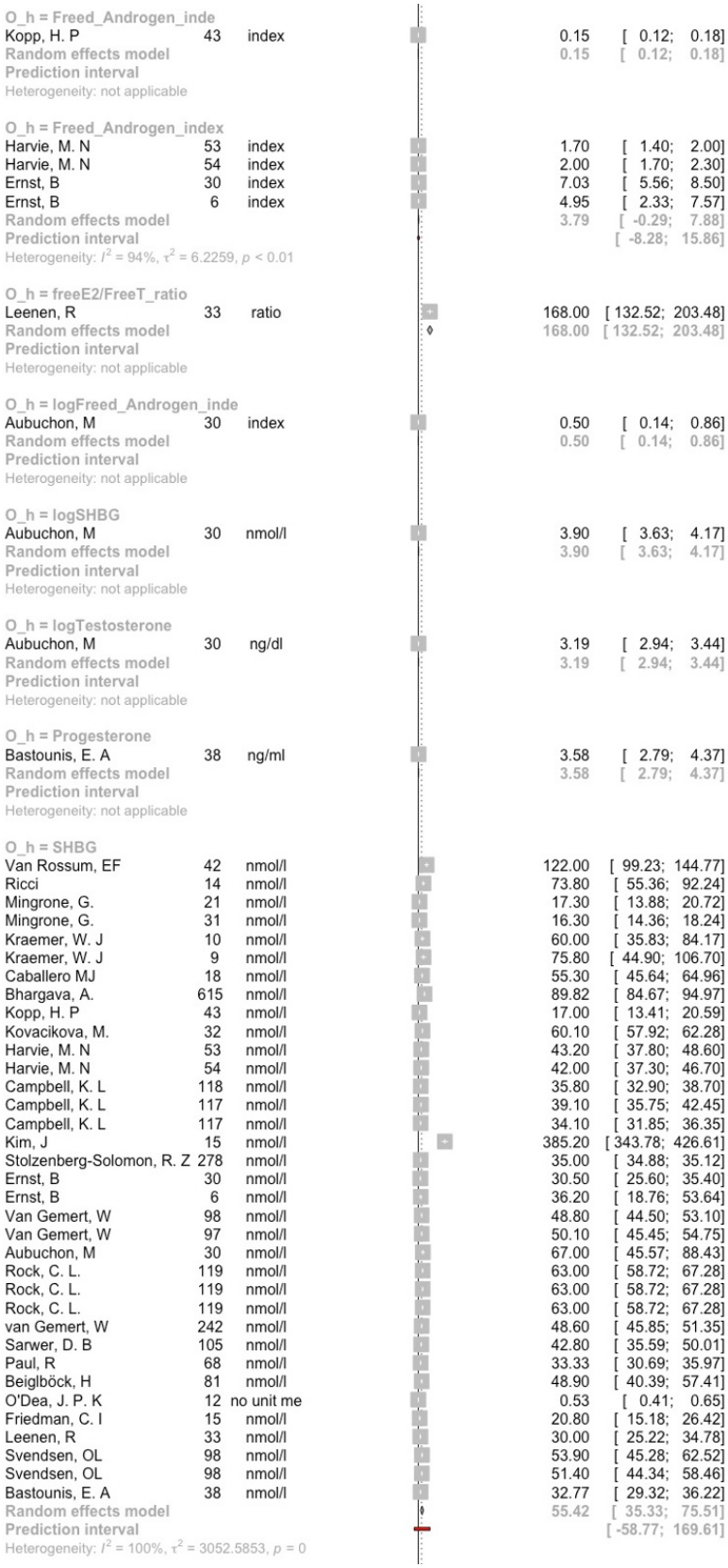


Figure 4.5.: Baseline anthropometric data of lifestyle interventions


Author n unit mean mean 95%-CI
O_h = Androstendione
Di Carlo 8 ng/ml 157.40 [144.79; 170.01]
Kopp, H. P 43 ng/ml 2.05 [1.82; 2.28]
Harvie, M. N 53 ng/ml 773.64 [688.01; 859.27]
Harvie, M. N 54 ng/ml 888.25 [802.66; 973.85]
Campbell, K. L 118 ng/ml 0.51 [0.47; 0.55]
Campbell, K. L 117 ng/ml 0.50 [0.46; 0.54]
Campbell, K. L 117 ng/ml 0.53 [0.49; 0.56]
Stolzenberg-Solomon, R. Z 278 ng/ml 0.44 [0.44; 0.44]
Van Gemert, W 98 ng/ml 0.56 [0.49; 0.62]
Van Gemert, W 97 ng/ml 0.56 [0.50; 0.62]
Beiglböck, H 81 ng/ml 1.24 [1.09; 1.39]
Svendsen, OL 98 ng/ml 0.72 [0.60; 0.83]
Svendsen, OL 98 ng/ml 0.74 [0.63; 0.86]
Bastounis, E. A 38 ng/ml 1.78 [1.49; 2.07]
Random effects model 128.49 [-43.67; 300.65]
Prediction interval [-538.28; 795.26]
Heterogeneity: I^2 = 99%, τ^2 = 87300.7118, p = 0
O_h = Cortisol/DHEAS molar ratio
Savastano, S 30 ratio 198.50 [177.21; 219.79]
Random effects model 198.50 [177.21; 219.79]
Prediction interval
Heterogeneity: not applicable
O_h = DHEAS
Di Carlo 8 µg/ml 1.18 [1.04; 1.32]
Savastano, S 30 µg/ml 0.99 [0.89; 1.10]
Kopp, H. P 43 µg/ml 0.63 [0.54; 0.73]
Harvie, M. N 53 µg/ml 1.18 [1.01; 1.34]
Harvie, M. N 54 µg/ml 1.25 [1.10; 1.40]
Stolzenberg-Solomon, R. Z 278 µg/ml 0.47 [0.47; 0.47]
Ernst, B 30 µg/ml 1.29 [1.00; 1.58]
Ernst, B 6 µg/ml 1.03 [0.53; 1.53]
Swora-Cwynar, E 39 µg/ml 2.96 [2.58; 3.35]
Sarwer, D. B 105 µg/ml 1.20 [1.03; 1.36]
Beiglböck, H 81 µg/ml 1.37 [1.23; 1.51]
Leenen, R 33 µg/ml 1.95 [1.65; 2.25]
Bastounis, E. A 38 µg/ml 2.22 [1.75; 2.69]
Random effects model 1.35 [0.95; 1.74]
Prediction interval [-0.11; 2.80]
Heterogeneity: I^2 = 99%, τ^2 = 0.4037, p < 0.01
O_h = Estradiol
Di Carlo 8 pg/ml 65.30 [52.62; 77.98]
Bhargava, A. 615 pg/ml 54.65 [48.15; 61.14]
Riedt, C. S 21 pg/ml 53.90 [34.35; 73.45]
Campbell, K. L 118 pg/ml 11.60 [10.70; 12.50]
Campbell, K. L 117 pg/ml 11.50 [10.55; 12.45]
Campbell, K. L 117 pg/ml 11.50 [10.55; 12.45]
Stolzenberg-Solomon, R. Z 278 pg/ml 9.40 [9.36; 9.44]
Van Gemert, W 98 pg/ml 3.70 [3.31; 4.09]
Van Gemert, W 97 pg/ml 4.15 [3.63; 4.67]
Swora-Cwynar, E 39 pg/ml 89.00 [68.66; 109.34]
O'Dea, J. P. K 12 pg/ml 35.00 [30.36; 39.64]
Boyden, T. W. 19 pg/ml 70.60 [43.36; 97.84]
Leenen, R 33 pg/ml 69.09 [55.82; 82.36]
Svendsen, OL 98 pg/ml 0.02 [-0.02; 0.05]
Svendsen, OL 98 pg/ml 0.02 [-0.03; 0.06]
Bastounis, E. A 38 pg/ml 94.85 [83.93; 105.77]
Random effects model 35.53 [17.55; 53.51]
Prediction interval [-37.82; 108.89]
Heterogeneity: I^2 = 100%, τ^2 = 1098.5580, p = 0
O_h = Estradiol_free
Campbell, K. L 118 pg/ml 0.31 [0.28; 0.34]
Campbell, K. L 117 pg/ml 0.30 [0.27; 0.33]
Campbell, K. L 117 pg/ml 0.32 [0.29; 0.35]
Stolzenberg-Solomon, R. Z 278 pg/ml 0.26 [0.26; 0.26]
Van Gemert, W 98 pg/ml 0.09 [0.08; 0.10]
Van Gemert, W 97 pg/ml 0.10 [0.08; 0.12]
van Gemert, W 236 pg/ml 0.09 [0.08; 0.10]
Leenen, R 33 pg/ml 1.36 [1.12; 1.60]
Random effects model 0.34 [0.00; 0.68]
Prediction interval [-0.67; 1.36]
Heterogeneity: I^2 = 100%, τ^2 = 0.1522, p = 0
O_h = Estrone
Ricci 14 ng/dl 2.55 [1.81; 3.29]
Riedt, C. S 21 ng/dl 6.96 [4.51; 9.41]
Campbell, K. L 118 ng/dl 3.52 [3.26; 3.78]
Campbell, K. L 117 ng/dl 3.48 [3.23; 3.73]
Campbell, K. L 117 ng/dl 3.39 [3.14; 3.64]
Stolzenberg-Solomon, R. Z 278 ng/dl 3.81 [3.80; 3.82]
Van Gemert, W 98 ng/dl 1.93 [1.76; 2.10]
Van Gemert, W 97 ng/dl 2.04 [1.88; 2.20]
Boyden, T. W. 19 ng/dl 5.26 [4.63; 5.89]
Leenen, R 33 ng/dl 5.83 [5.22; 6.44]
Random effects model 3.73 [2.63; 4.83]
Prediction interval [0.27; 7.19]
Heterogeneity: I^2 = 99%, τ^2 = 2.0130, p < 0.01


O_h = Freed_Androgen_inde
Kopp, H. P 43 index 0.15 [0.12; 0.18]
Random effects model 0.15 [0.12; 0.18]
Prediction interval
Heterogeneity: not applicable
O_h = Freed_Androgen_index
Harvie, M. N 53 index 1.70 [1.40; 2.00]
Harvie, M. N 54 index 2.00 [1.70; 2.30]
Ernst, B 30 index 7.03 [5.56; 8.50]
Ernst, B 6 index 4.95 [2.33; 7.57]
Random effects model 3.79 [-0.29; 7.88]
Prediction interval [-8.28; 15.86]
Heterogeneity: I^2 = 94%, τ^2 = 6.2259, p < 0.01
O_h = freeE2/FreeT_ratio
Leenen, R 33 ratio 168.00 [132.52; 203.48]
Random effects model 168.00 [132.52; 203.48]
Prediction interval
Heterogeneity: not applicable
O_h = logFreed_Androgen_inde
Aubuchon, M 30 index 0.50 [0.14; 0.86]
Random effects model 0.50 [0.14; 0.86]
Prediction interval
Heterogeneity: not applicable
O_h = logSHBG
Aubuchon, M 30 nmol/l 3.90 [3.63; 4.17]
Random effects model 3.90 [3.63; 4.17]
Prediction interval
Heterogeneity: not applicable
O_h = logTestosterone
Aubuchon, M 30 ng/dl 3.19 [2.94; 3.44]
Random effects model 3.19 [2.94; 3.44]
Prediction interval
Heterogeneity: not applicable
O_h = Progesterone
Bastounis, E. A 38 ng/ml 3.58 [2.79; 4.37]
Random effects model 3.58 [2.79; 4.37]
Prediction interval
Heterogeneity: not applicable
O_h = SHBG
Van Rossum, EF 42 nmol/l 122.00 [99.23; 144.77]
Ricci 14 nmol/l 73.80 [55.36; 92.24]
Mingrone, G. 21 nmol/l 17.30 [13.88; 20.72]
Mingrone, G. 31 nmol/l 16.30 [14.36; 18.24]
Kraemer, W. J 10 nmol/l 60.00 [35.83; 84.17]
Kraemer, W. J 9 nmol/l 75.80 [44.90; 106.70]
Caballero MJ 18 nmol/l 55.30 [45.64; 64.96]
Bhargava, A. 615 nmol/l 89.82 [84.67; 94.97]
Kopp, H. P 43 nmol/l 17.00 [13.41; 20.59]
Kovacikova, M. 32 nmol/l 60.10 [57.92; 62.28]
Harvie, M. N 53 nmol/l 43.20 [37.80; 48.60]
Harvie, M. N 54 nmol/l 42.00 [37.30; 46.70]
Campbell, K. L 118 nmol/l 35.80 [32.90; 38.70]
Campbell, K. L 117 nmol/l 39.10 [35.75; 42.45]
Campbell, K. L 117 nmol/l 34.10 [31.85; 36.35]
Kim, J 15 nmol/l 385.20 [343.78; 426.61]
Stolzenberg-Solomon, R. Z 278 nmol/l 35.00 [34.88; 35.12]
Ernst, B 30 nmol/l 30.50 [25.60; 35.40]
Ernst, B 6 nmol/l 36.20 [18.76; 53.64]
Van Gemert, W 98 nmol/l 48.80 [44.50; 53.10]
Van Gemert, W 97 nmol/l 50.10 [45.45; 54.75]
Aubuchon, M 30 nmol/l 67.00 [45.57; 88.43]
Rock, C. L. 119 nmol/l 63.00 [58.72; 67.28]
Rock, C. L. 119 nmol/l 63.00 [58.72; 67.28]
Rock, C. L. 119 nmol/l 63.00 [58.72; 67.28]
van Gemert, W 242 nmol/l 48.60 [45.85; 51.35]
Sarwer, D. B 105 nmol/l 42.80 [35.59; 50.01]
Paul, R 68 nmol/l 33.33 [30.69; 35.97]
Beiglböck, H 81 nmol/l 48.90 [40.39; 57.41]
O'Dea, J. P. K 12 no unit me 0.53 [0.41; 0.65]
Friedman, C. I 15 nmol/l 20.80 [15.18; 26.42]
Leenen, R 33 nmol/l 30.00 [25.22; 34.78]
Svendsen, OL 98 nmol/l 53.90 [45.28; 62.52]
Svendsen, OL 98 nmol/l 51.40 [44.34; 58.46]
Bastounis, E. A 38 nmol/l 32.77 [29.32; 36.22]
Random effects model 55.42 [35.33; 75.51]
Prediction interval [-58.77; 169.61]
Heterogeneity: I^2 = 100%, τ^2 = 3052.5853, p = 0

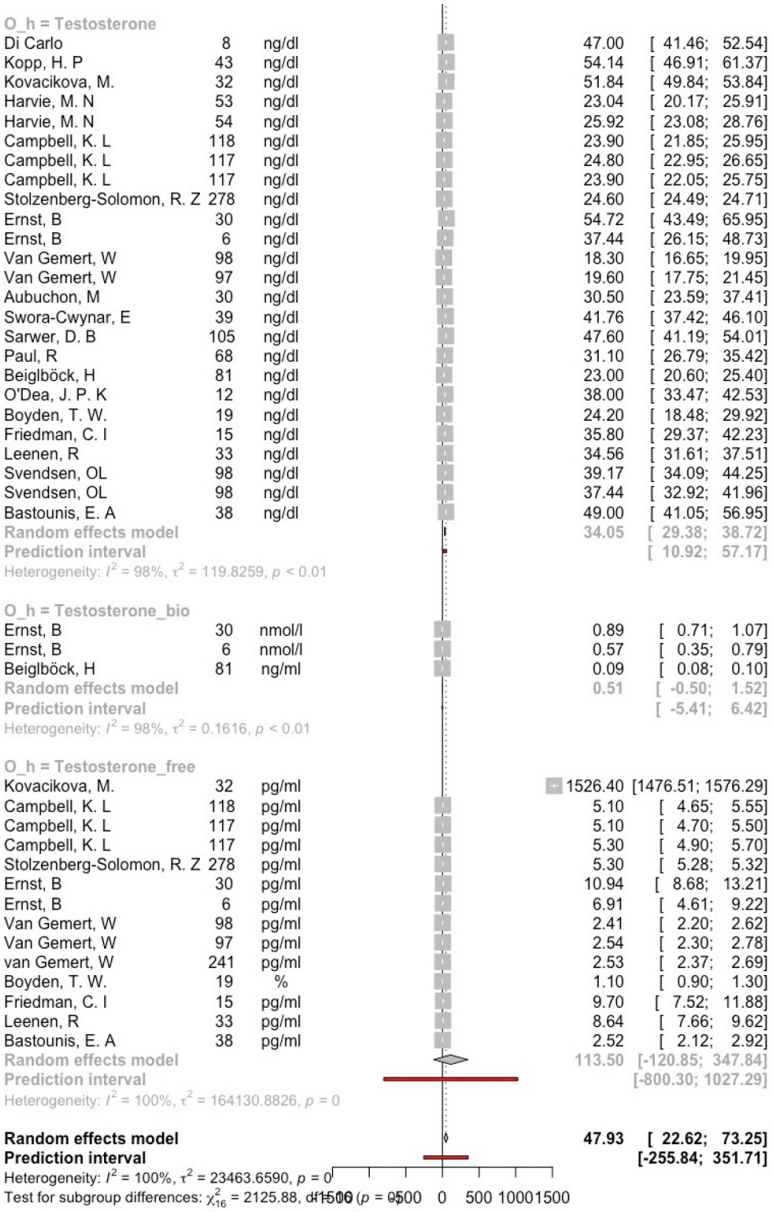


Figure 4.6.: Baseline sex steroids (surgical and lifestyle interventions)

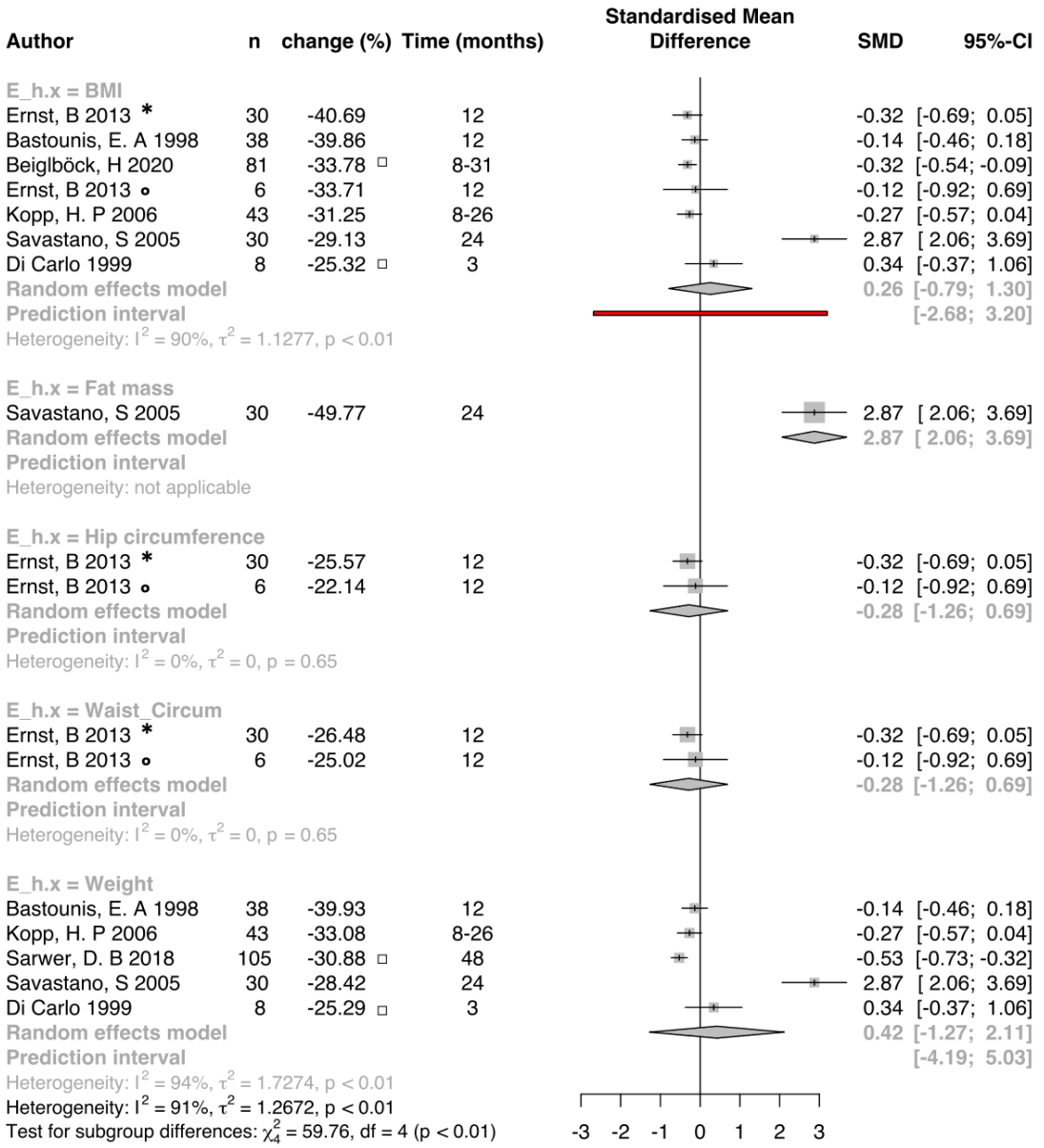


Figure 4.7.: DHEAS in surgical interventions. * premenopausal women;° postmenopausal women; □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

further investigate. In the subgroup analysis of BMI, Savastano et al. (2005) was defined as an outlier. The results after the recalculation show a statistically significant predicted SMD of -0.24 with a 95% CI (-0.40; -0.08). Those results do not differ as much from the SMD of the individual studies, and show a reduction in DHEAS after a surgical weight loss intervention. Moreover, a change in heterogeneity measures can be observed. I^2 changed from 90% to 0%, τ^2 from 1.13 to 0, and the p value from p<0.01 to p<0.59.

In the analysis for weight, 5 studies are included, manly overlapping with those included in the BMI subgroup analysis. The overall SMD was 0.42 95%CI (-1.27; 2.11). Three studies have a negative SMD, Di Carlo et al. (1999) and Savastano et al. (2005) again differ with a positive SMD. As with the analysis for BMI, high heterogeneity in results between studies was observed for weight with an I^2 of 94% and τ^2 = 1.73.

Lifestyle interventions

In Figure 4.8, we show the forest plot for DHEAS including studies with lifestyle interventions. The anthropometric measures with sufficient data to meta-analyse were change in percent body fat, fat mass and weight. The analysis for percent body fat includes 3 studies and shows a negative SMD of -0.14 (-0.67; 0.40), though this did not reach statistical significance. The SMDs of the individual studies report a negative SMD, even though one study shows a positive SMD. For this analysis, the I^2 is 52% and τ^2 is 0.02. The other two analysis show a positive overall SMD, 0.07 (-0.71; 0.86) for fat mass (4 studies) and 0.15 (-0.41; 0.72)for weight (5 studies). These positive SMDs are caused by additional studies included in the analysis that individually show a positive SMD. Therefore, for the analysis of those anthropometric measures, a higher heterogeneity can be observed. In our analysis for fat mass the I^2 is 86% and the τ^2 is 0.21, for weight the I^2 is 90% and the τ^2 is 0.18. An association between decrease in DHEAS and decrease in percent body fat, fat mass and weight as a result of lifestyle interventions, was found in the study of Swora-Cwynar et al. (2016). An association between decrease in DHEAS and increase in fat mass and weight for the studies of Leenen et al. (1994) and Stolzenberg-Solomon et al. (2012). No association is shown for both groups of the study conducted by Harvie et al. (2011). Additionally, the results for all subgroup analyses display a similar pattern, as the studies with the highest decrease of examined anthropometric data had the highest positive SMD for DHEAS change, and the studies with the least decrease had the highest negative SMD.

Narrative summary

Additional studies, that were not amenable to meta-analyse, were identified. The study by Sarwer et al. (2014), included in narrative summary because it is the same study as Sarwer et al. (2018), investigated the effect of a surgical intervention on DHEAS. Their results show an association between weight loss and decrease in DHEAS. Goodfriend et al. (1999) conducted a lifestyle intervention and did not find an association between decrease in BMI or VAT and change in DHEAS. This study is included in the narrative summary because they did not specify if body composition measure were only assessed in women or both in men and women. In addition, not all values were reported in this study. The lifestyle intervention study of McTiernan et al. (2004a)

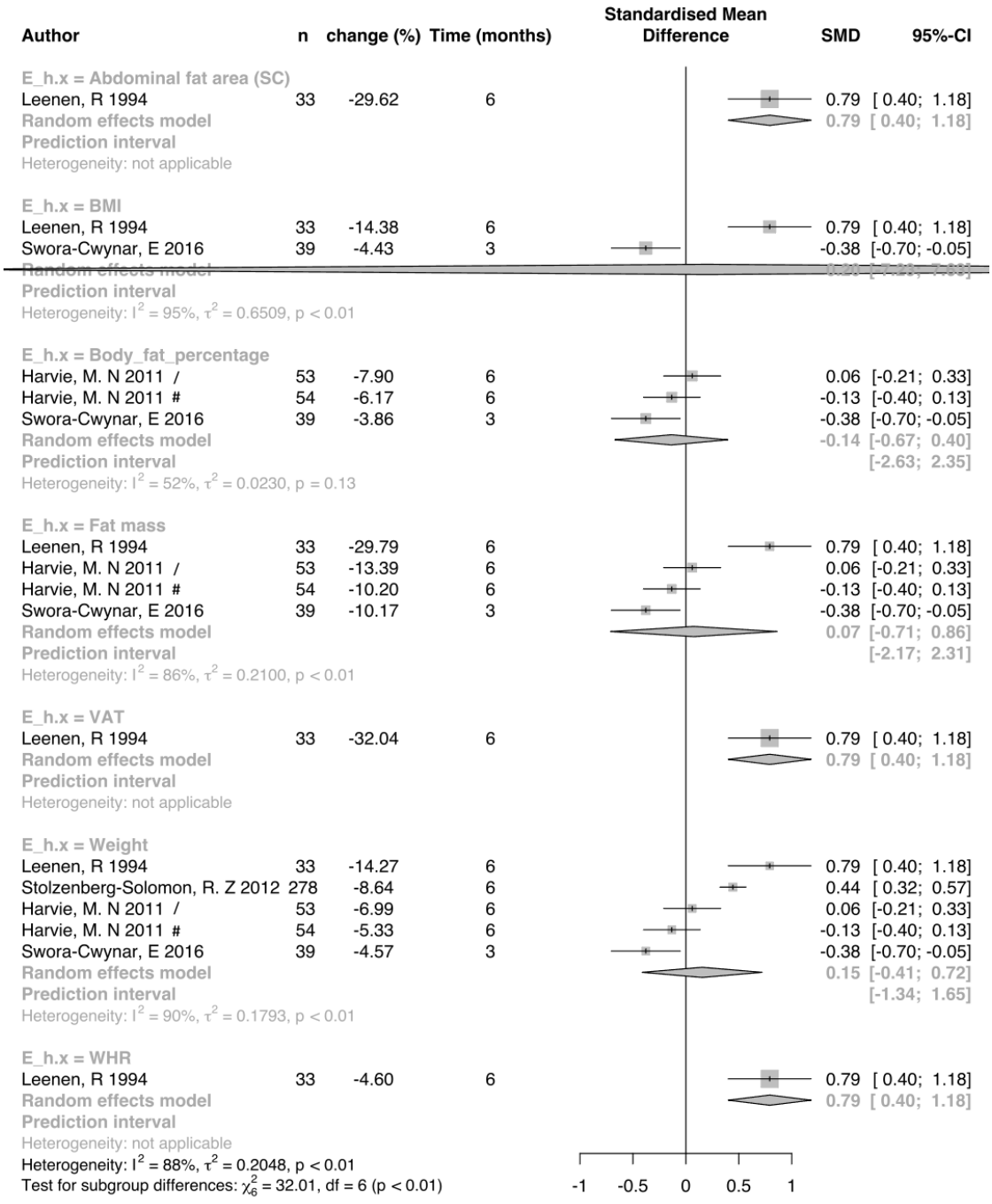


Figure 4.8.: DHEAS in lifestyle interventions. # continuous energy restriction; / intermittent continuous energy; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

also found no association between decrease of > 2 percent body fat and decrease in DHEAS. This study was included in the narrative summary, as only the group with a decrease of > 2 percent body fat was relevant for our study.

Summary

Our analysis shows, that in the surgical intervention studies, no association was observed between decrease in BMI or weight and circulating concentrations of DHEAS. Similarly, change in percent body fat, fat mass or weight as a result of a lifestyle intervention was not associated with a change in DHEAS.

4.2.2. SHBG

Surgical interventions

Figure 4.9 shows the change in SHBG with multiple types of anthropometric measurements for studies with a surgical intervention. The anthropometric measures that are amenable to meta-analysis within the surgical interventions (i.e., 3 studies) are BMI and weight. Seven studies are included in the analysis for BMI. All studies individually show a positive SMD, resulting in a statistically significant overall SMD of 3.12 95 (2.14; 4.09). This shows that BMI change, as a result of surgical intervention, led to an increase in SHBG in the investigated studies. An I^2 of 93% and τ^2 of 0.99 was observed, indicating a high between study heterogeneity. Beiglböck et al. (2020) was defined as an outlier in the BMI subgroup. When Beiglböck et al. (2020) was removed from the analysis, the SMD increased to 3.45 (2.74;4.17), I^2 decreased to 51% and tau2 decreased to 0.23. This showed an even stronger effect of decrease of BMI through surgical intervention on the change of SHBG.
In the analysis for weight, of the 6 studies that are included, 4 are also included in the analysis for BMI. Similar to the analysis for BMI, the overall SMD of 2.81 (1.27; 4.35) is clearly positive and statistically significant. The heterogeneity between the studies was high, with an I^2 of 95% and a τ^2 of 2.00. Nevertheless, an association between weight loss and increase in SHBG was observed.

Lifestyle interventions

In Figure 4.10 we present the analysis for SHBG in lifestyle interventions. The analysis for change in BMI includes 8 studies with an overall SMD of 0.53 (-0.06; 1.12), however, no statistical significance was identified. All the individual studies show a rather similar (0.16-0.50) positive SMD, except for, Kovacikova et al. (2008) which has a higher value (2.44). Relatively high heterogeneity was observed, with an I^2 of 84% and τ^2 of 0.39. The study of Kovacikova et al. (2008) was detected as an outlier. When this study was excluded from the analysis, the SMD decreased to 0.29 (0.20; 0.38), which indicated an attenuated association. Also, the heterogeneity decreased to I^2 of 0.00% and τ^2 of 0.001. Thirteen studies were included in the analysis for percent body fat. The overall SMD of 0.26 (0.10; 0.42) is significantly positive. The SMDs of the individual studies are close together, although 2 studies report a negative SMD. For the subgroup analysis for percent body fat, the I^2 is 73% and the τ^2 is 0.05. For the subgroup of

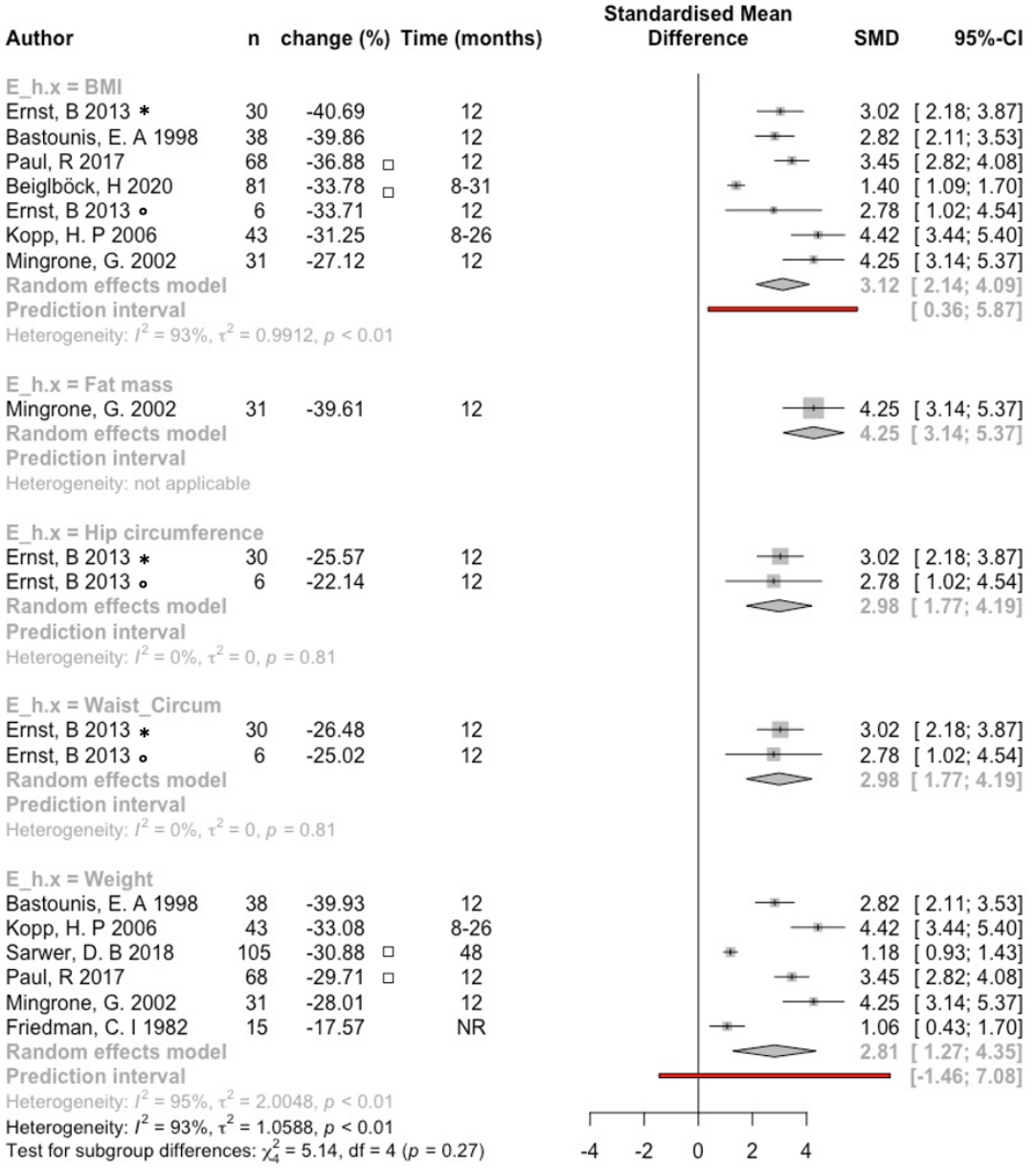
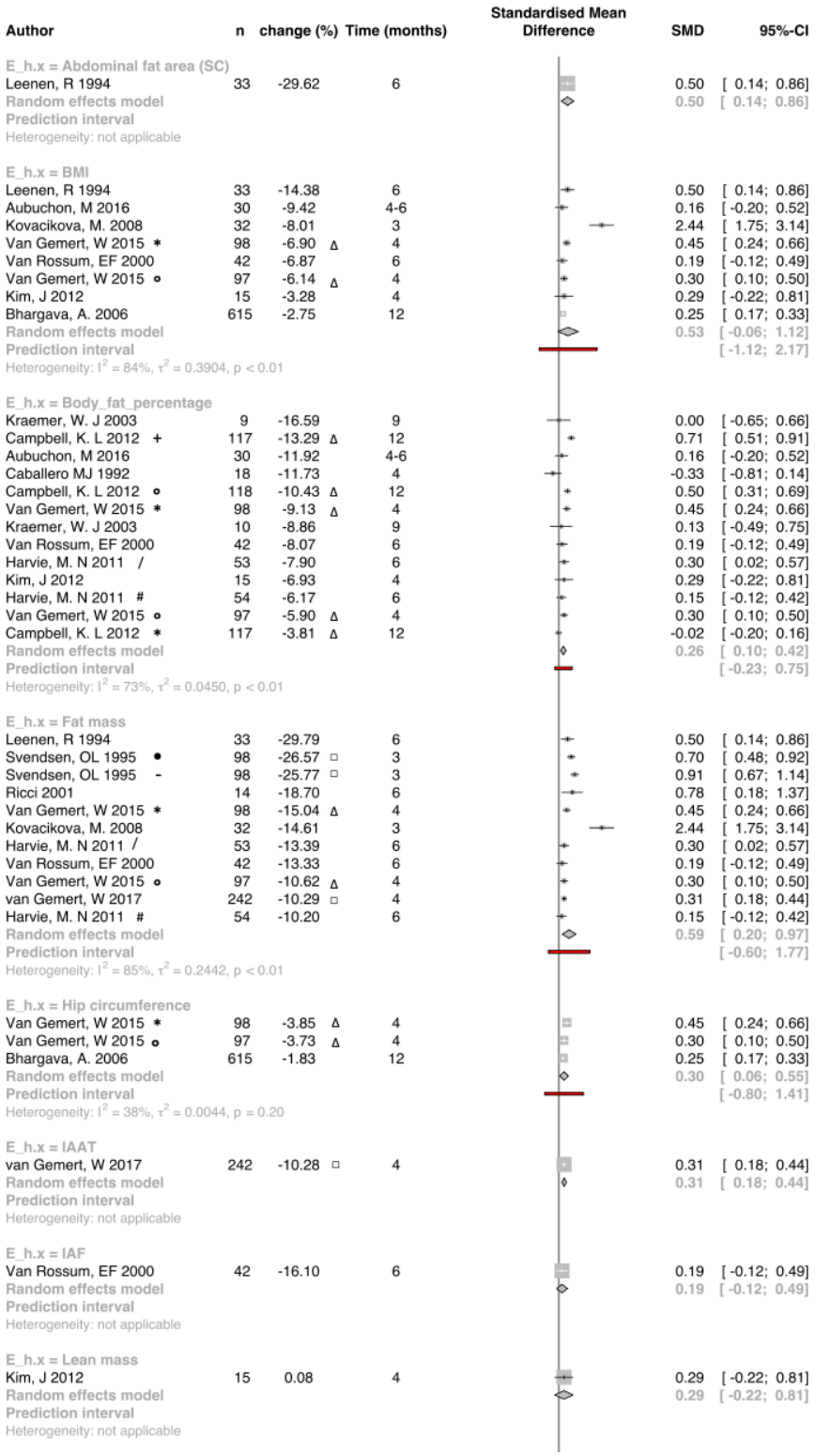


Figure 4.9.: SHBG in surgical interventions. Duration not reported (NR) but a mean of 7.9 months until stable weight loss; * premenopausal women;° postmenopausal women; □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed


Author
n
change (%)
Time (months)
Standardised Mean Difference
SMD
95%-CI
E_h.x = Abdominal fat area (SC)
Leenen, R 1994 33 -29.62 6 0.50 [0.14; 0.86]
Random effects model 0.50 [0.14; 0.86]
Prediction interval
Heterogeneity: not applicable
E_h.x = BMI
Leenen, R 1994 33 -14.38 6 0.50 [0.14; 0.86]
Aubuchon, M 2016 30 -9.42 4-6 0.16 [-0.20; 0.52]
Kovacikova, M. 2008 32 -8.01 3 2.44 [1.75; 3.14]
Van Gemert, W 2015 * 98 -6.90 Δ 4 0.45 [0.24; 0.66]
Van Rossum, EF 2000 42 -6.87 6 0.19 [-0.12; 0.49]
Van Gemert, W 2015 ∘ 97 -6.14 Δ 4 0.30 [0.10; 0.50]
Kim, J 2012 15 -3.28 4 0.29 [-0.22; 0.81]
Bhargava, A. 2006 615 -2.75 12 0.25 [0.17; 0.33]
Random effects model 0.53 [-0.06; 1.12]
Prediction interval [-1.12; 2.17]
Heterogeneity: I^2 = 84%, τ^2 = 0.3904, p < 0.01
E_h.x = Body_fat_percentage
Kraemer, W. J 2003 9 -16.59 9 0.00 [-0.65; 0.66]
Campbell, K. L 2012 + 117 -13.29 Δ 12 0.71 [0.51; 0.91]
Aubuchon, M 2016 30 -11.92 4-6 0.16 [-0.20; 0.52]
Caballero MJ 1992 18 -11.73 4 -0.33 [-0.81; 0.14]
Campbell, K. L 2012 ∘ 118 -10.43 Δ 12 0.50 [0.31; 0.69]
Van Gemert, W 2015 * 98 -9.13 Δ 4 0.45 [0.24; 0.66]
Kraemer, W. J 2003 10 -8.86 9 0.13 [-0.49; 0.75]
Van Rossum, EF 2000 42 -8.07 6 0.19 [-0.12; 0.49]
Harvie, M. N 2011 / 53 -7.90 6 0.30 [0.02; 0.57]
Kim, J 2012 15 -6.93 4 0.29 [-0.22; 0.81]
Harvie, M. N 2011 # 54 -6.17 6 0.15 [-0.12; 0.42]
Van Gemert, W 2015 ∘ 97 -5.90 Δ 4 0.30 [0.10; 0.50]
Campbell, K. L 2012 * 117 -3.81 Δ 12 -0.02 [-0.20; 0.16]
Random effects model 0.26 [0.10; 0.42]
Prediction interval [-0.23; 0.75]
Heterogeneity: I^2 = 73%, τ^2 = 0.0450, p < 0.01
E_h.x = Fat mass
Leenen, R 1994 33 -29.79 6 0.50 [0.14; 0.86]
Svendsen, OL 1995 ● 98 -26.57 □ 3 0.70 [0.48; 0.92]
Svendsen, OL 1995 - 98 -25.77 □ 3 0.91 [0.67; 1.14]
Ricci 2001 14 -18.70 6 0.78 [0.18; 1.37]
Van Gemert, W 2015 * 98 -15.04 Δ 4 0.45 [0.24; 0.66]
Kovacikova, M. 2008 32 -14.61 3 2.44 [1.75; 3.14]
Harvie, M. N 2011 / 53 -13.39 6 0.30 [0.02; 0.57]
Van Rossum, EF 2000 42 -13.33 6 0.19 [-0.12; 0.49]
Van Gemert, W 2015 ∘ 97 -10.62 Δ 4 0.30 [0.10; 0.50]
van Gemert, W 2017 242 -10.29 □ 4 0.31 [0.18; 0.44]
Harvie, M. N 2011 # 54 -10.20 6 0.15 [-0.12; 0.42]
Random effects model 0.59 [0.20; 0.97]
Prediction interval [-0.60; 1.77]
Heterogeneity: I^2 = 85%, τ^2 = 0.2442, p < 0.01
E_h.x = Hip circumference
Van Gemert, W 2015 * 98 -3.85 Δ 4 0.45 [0.24; 0.66]
Van Gemert, W 2015 ∘ 97 -3.73 Δ 4 0.30 [0.10; 0.50]
Bhargava, A. 2006 615 -1.83 12 0.25 [0.17; 0.33]
Random effects model 0.30 [0.06; 0.55]
Prediction interval [-0.80; 1.41]
Heterogeneity: I^2 = 38%, τ^2 = 0.0044, p = 0.20
E_h.x = IAAT
van Gemert, W 2017 242 -10.28 □ 4 0.31 [0.18; 0.44]
Random effects model 0.31 [0.18; 0.44]
Prediction interval
Heterogeneity: not applicable
E_h.x = IAF
Van Rossum, EF 2000 42 -16.10 6 0.19 [-0.12; 0.49]
Random effects model 0.19 [-0.12; 0.49]
Prediction interval
Heterogeneity: not applicable
E_h.x = Lean mass
Kim, J 2012 15 0.08 4 0.29 [-0.22; 0.81]
Random effects model 0.29 [-0.22; 0.81]
Prediction interval
Heterogeneity: not applicable

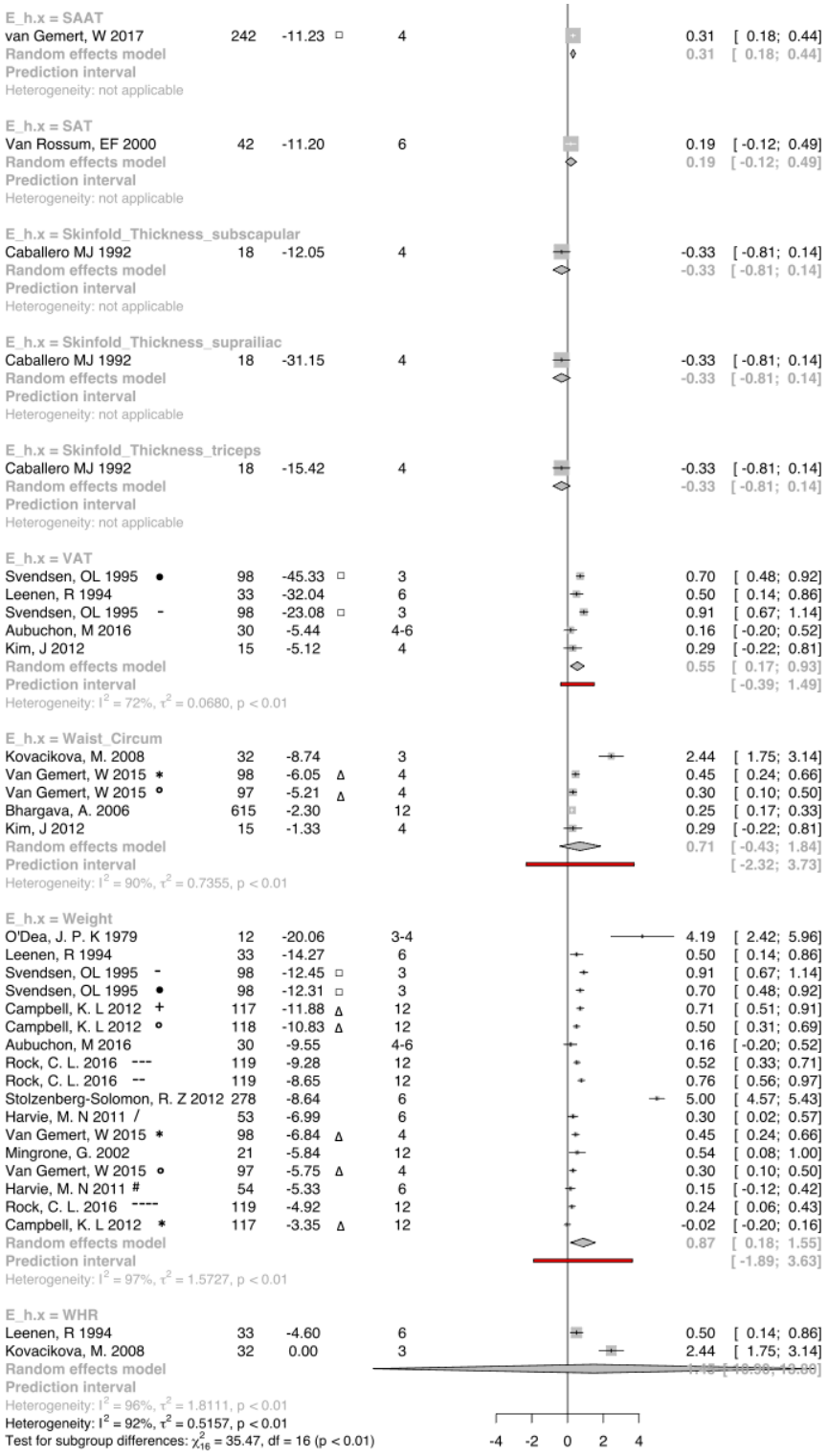


Figure 4.10.: SHBG in lifestyle interventions. * exercise; ° diet; + exercisediet mixed; - android; • gynoid; Δ significant compared to control group; □ not mentioned if significant; # continuous energy restriction; / intermittent continuous energy; – low-fat insulin sensitive; — walnut insulin sensitive; —- low-carb insulin sensitive; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

percent body fat, the diet + exercise intervention group of Campbell et al. (2012) was defined as an outlier, which exclusion would lead to an overall SMD of 0.22 (0.08; 0.36), I^2 would decrease to 58% and τ^2 to 0.03. The 11 studies included in the analysis for fat mass all showed a positive SMD, with a significant overall SMD of 0.59 (0.20; 0.97). This analysis showed a high heterogeneity as well, with an I^2 of 85% and τ^2 of 0.24, possibly because of the high SMD of Kovacikova et al. (2008). Kovacikova et al. (2008) was identified as an outlier in the analysis for fat mass. The overall SMD without this study would decrease to 0.44 (0.26; 0.62), I^2 would decrease to 74.7% and τ^2 to 0.05. The most studies, 17, are included in the analysis for weight. The overall SMD of 0.87 (0.18; 1.55) for this subgroup is statistically significant. In general, the individual associations observed in each study look in line with each other, except for O'dea et al. (1979) and Stolzenberg-Solomon et al. (2012) with a SMD of 4.19 and 5.00. A high heterogeneity where I^2 is 97% and τ^2 is 1.57 can be observed. This heterogeneity is likely to be caused by O'dea et al. (1979) and Stolzenberg-Solomon et al. (2012). In the analysis for weight, the studies of O'dea et al. (1979), Stolzenberg-Solomon et al. (2012) and Campbell et al. (2012) (exercise group) were defined as outliers. The result without those studies would show that the SMD decreased to 0.49 (0.35; 0.62), the I^2 decreased to 73.4% and τ^2 to 0.04.

The results for the analysis for hip circumference, show a statistically significant overall SMD of 0.30 (0.06; 0.55). The analysis for VAT and Waist circumference report a statically significant overall SMD of 0.55 (0.17; 0.93) for VAT and a positive but not significant overall SMD of 0.71 (-0.43; 1.84) for Waist circumference.

All studies included in the analysis report a decrease in the types of anthropometric measures and calculations that were meta-analysed. Even though, the studies of Campbell et al. (2012) (exercise group) and Caballero and Maynar (1992) reported a negative SMD, no associations were found between decrease in anthropometric data and decrease in SHBG. For all the other studies, either an association between decrease in anthropometric data and increase in SHBG or no association was found. Our results indicate an inverse association between decrease in percent body fat, fat mass, hip circumference, VAT, or weight and change in SHBG.

Narrative summary

Further studies, that were not amenable to meta-analyse, were identified and described in a narrative way. Sarwer et al. (2014), who was included in the narrative summary because it is the same study as Sarwer et al. (2018), investigated the effect of a surgical intervention on SHBG and found an association between weight loss and increase in SHBG. Linkov et al. (2017) also conducted a surgical intervention and found an association between decrease in weight, BMI or WC and increase in SHBG. This study was included in the narrative summary, as no specific values for SHBG were reported. Similarly, the lifestyle intervention of Friedenreich et al. (2010), included in narrative summary as only change of weight is reported, found an association between decrease in weight and increase in SHBG. The lifestyle intervention of Duggan et al. (2019) also reported an association between weight loss of > 10 percent and increase in SHBG. This study was included in narrative summary, as only the group with > 10 weight loss was relevant for our

study. A lifestyle intervention was also conducted in the study of Kaaks et al. (2003), included in the narrative summary because no measure of variance was reported. The results of this study showed an association between decrease in BMI, WHR, WC or hip circumference and increase in SHBG. However, the lifestyle interventions of Monninkhof et al. (2009), included in the narrative summary because no measure of variance was reported, and McTiernan et al. (2004a), included in the narrative summary as only the group with a decrease of > 2 percent body fat was relevant for our study, reported no association between decrease of > 2 percent body fat and change in SHBG.

Summary

Both intervention types show an association between decrease in anthropometric data and change in SHBG. The surgical intervention studies report a higher increase in SHBG with change in body composition, compared to lifestyle interventions.

4.2.3. Testosterone

Surgical interventions

The change in testosterone by the type of anthropometric measures for surgical interventions studies is displayed in Figure 4.11. The analysis of BMI includes 7 studies that all show a negative SMD, except for the study of Di Carlo et al. (1999). The statistically significant overall SMD for this subgroup is -0.50 (-0.89;-0.12). Although Di Carlo et al. (1999) reports a positive SMD, the heterogeneity is rather moderate, with an I^2 of 64% and τ^2 of 0.07. Di Carlo et al. (1999) was defined as an outlier in the BMI analysis. When Di Carlo et al. (1999) was removed from the analysis, the SMD decreased to -0.58 (-0.77;-0.38). This would indicate an even stronger change in testosterone associated with decrease in BMI as a result of surgical intervention. Also, the heterogeneity between the studies would be smaller, with I^2 of 23.6% and τ^2 of 0.01. The analysis for weight includes 6 studies, which overlap for the most part with those included in the BMI group. In this analysis Di Carlo et al. (1999) is again the only study that reports a positive SMD. Also for this analysis, the overall SMD is negative, more specifically -0.42 (-0.99;0.15), but not significant. The between study heterogeneity is higher compared to the BMI analysis with I^2 of 76% and τ^2 of 0.19. For three studies, no association between decrease in body composition and change in testosterone is found. The other 6 studies report a positive association. Our subgroup analysis only shows an association for decrease in BMI and decrease in testosterone.

Lifestyle interventions

Figure 4.12 includes the change in testosterone by the type of anthropometric measure for lifestyle intervention studies. Five anthropometric parameters were amenable to meta-analyse including BMI, percent body fat, fat mass, VAT, waist circumference and weight. Between those analyses, there is a high overlap of the included studies. The analysis for the subgroup BMI includes 6 studies, which all report a negative SMD. The overall summary SMD of those studies is -0.41 (-0.80;-0.01), which is statistically significant. The results for the between study heterogeneity show an I^2 of 81% an τ^2 of 0.11. Nine studies are included in the analysis for percent body fat.

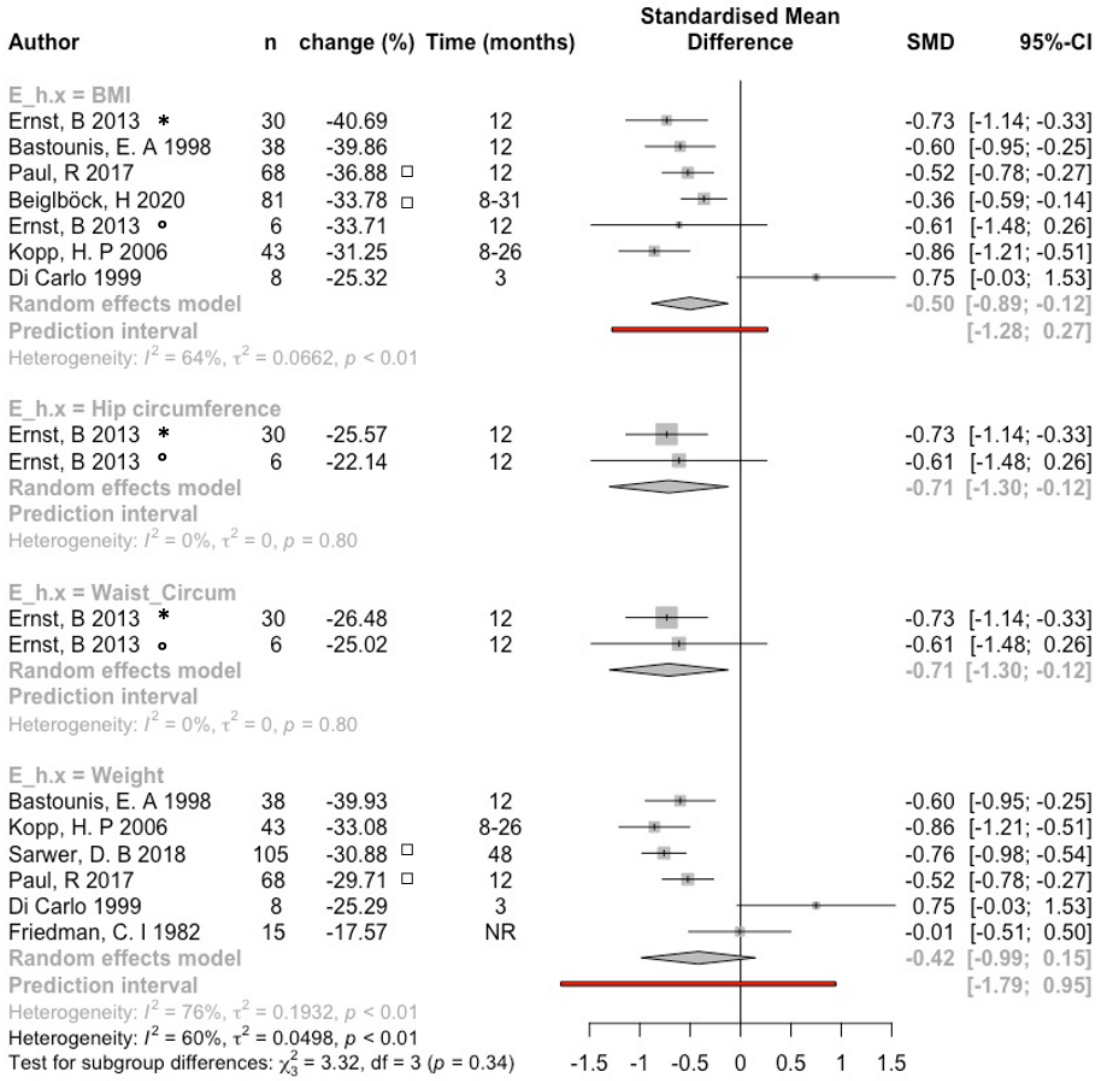
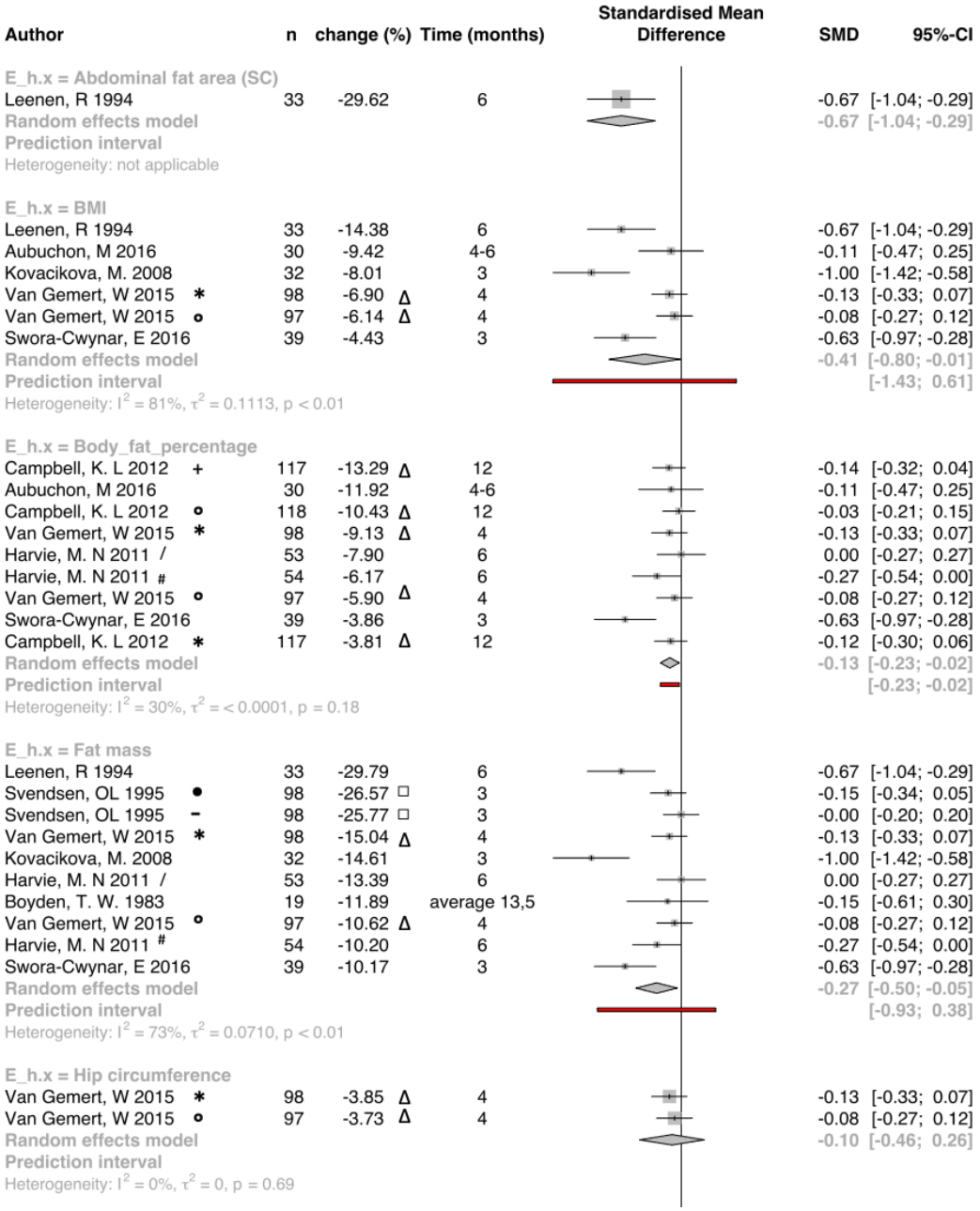


Figure 4.11.: Testosterone in surgical interventions. Duration not reported (NR) but a mean of 7.9 months until stable weight loss; * premenopausal women;° postmenopausal women; □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed


Author
n
change (%)
Time (months)
Standardised Mean Difference
SMD
95%-CI
E_h.x = Abdominal fat area (SC)
Leenen, R 1994 33 -29.62 6 -0.67 [-1.04; -0.29]
Random effects model -0.67 [-1.04; -0.29]
Prediction interval
Heterogeneity: not applicable
E_h.x = BMI
Leenen, R 1994 33 -14.38 6 -0.67 [-1.04; -0.29]
Aubuchon, M 2016 30 -9.42 4-6 -0.11 [-0.47; 0.25]
Kovacikova, M. 2008 32 -8.01 3 -1.00 [-1.42; -0.58]
Van Gemert, W 2015 * 98 -6.90 Δ 4 -0.13 [-0.33; 0.07]
Van Gemert, W 2015 ° 97 -6.14 Δ 4 -0.08 [-0.27; 0.12]
Swora-Cwynar, E 2016 39 -4.43 3 -0.63 [-0.97; -0.28]
Random effects model -0.41 [-0.80; -0.01]
Prediction interval [-1.43; 0.61]
Heterogeneity: I^2 = 81%, τ^2 = 0.1113, p < 0.01
E_h.x = Body_fat_percentage
Campbell, K. L 2012 + 117 -13.29 Δ 12 -0.14 [-0.32; 0.04]
Aubuchon, M 2016 30 -11.92 4-6 -0.11 [-0.47; 0.25]
Campbell, K. L 2012 ° 118 -10.43 Δ 12 -0.03 [-0.21; 0.15]
Van Gemert, W 2015 * 98 -9.13 Δ 4 -0.13 [-0.33; 0.07]
Harvie, M. N 2011 / 53 -7.90 6 0.00 [-0.27; 0.27]
Harvie, M. N 2011 # 54 -6.17 6 -0.27 [-0.54; 0.00]
Van Gemert, W 2015 ° 97 -5.90 Δ 4 -0.08 [-0.27; 0.12]
Swora-Cwynar, E 2016 39 -3.86 3 -0.63 [-0.97; -0.28]
Campbell, K. L 2012 * 117 -3.81 Δ 12 -0.12 [-0.30; 0.06]
Random effects model -0.13 [-0.23; -0.02]
Prediction interval [-0.23; -0.02]
Heterogeneity: I^2 = 30%, τ^2 = < 0.0001, p = 0.18
E_h.x = Fat mass
Leenen, R 1994 33 -29.79 6 -0.67 [-1.04; -0.29]
Svendsen, OL 1995 • 98 -26.57 □ 3 -0.15 [-0.34; 0.05]
Svendsen, OL 1995 – 98 -25.77 □ 3 -0.00 [-0.20; 0.20]
Van Gemert, W 2015 * 98 -15.04 Δ 4 -0.13 [-0.33; 0.07]
Kovacikova, M. 2008 32 -14.61 3 -1.00 [-1.42; -0.58]
Harvie, M. N 2011 / 53 -13.39 6 0.00 [-0.27; 0.27]
Boyden, T. W. 1983 19 -11.89 average 13,5 -0.15 [-0.61; 0.30]
Van Gemert, W 2015 ° 97 -10.62 Δ 4 -0.08 [-0.27; 0.12]
Harvie, M. N 2011 # 54 -10.20 6 -0.27 [-0.54; 0.00]
Swora-Cwynar, E 2016 39 -10.17 3 -0.63 [-0.97; -0.28]
Random effects model -0.27 [-0.50; -0.05]
Prediction interval [-0.93; 0.38]
Heterogeneity: I^2 = 73%, τ^2 = 0.0710, p < 0.01
E_h.x = Hip circumference
Van Gemert, W 2015 * 98 -3.85 Δ 4 -0.13 [-0.33; 0.07]
Van Gemert, W 2015 ° 97 -3.73 Δ 4 -0.08 [-0.27; 0.12]
Random effects model -0.10 [-0.46; 0.26]
Prediction interval
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.69

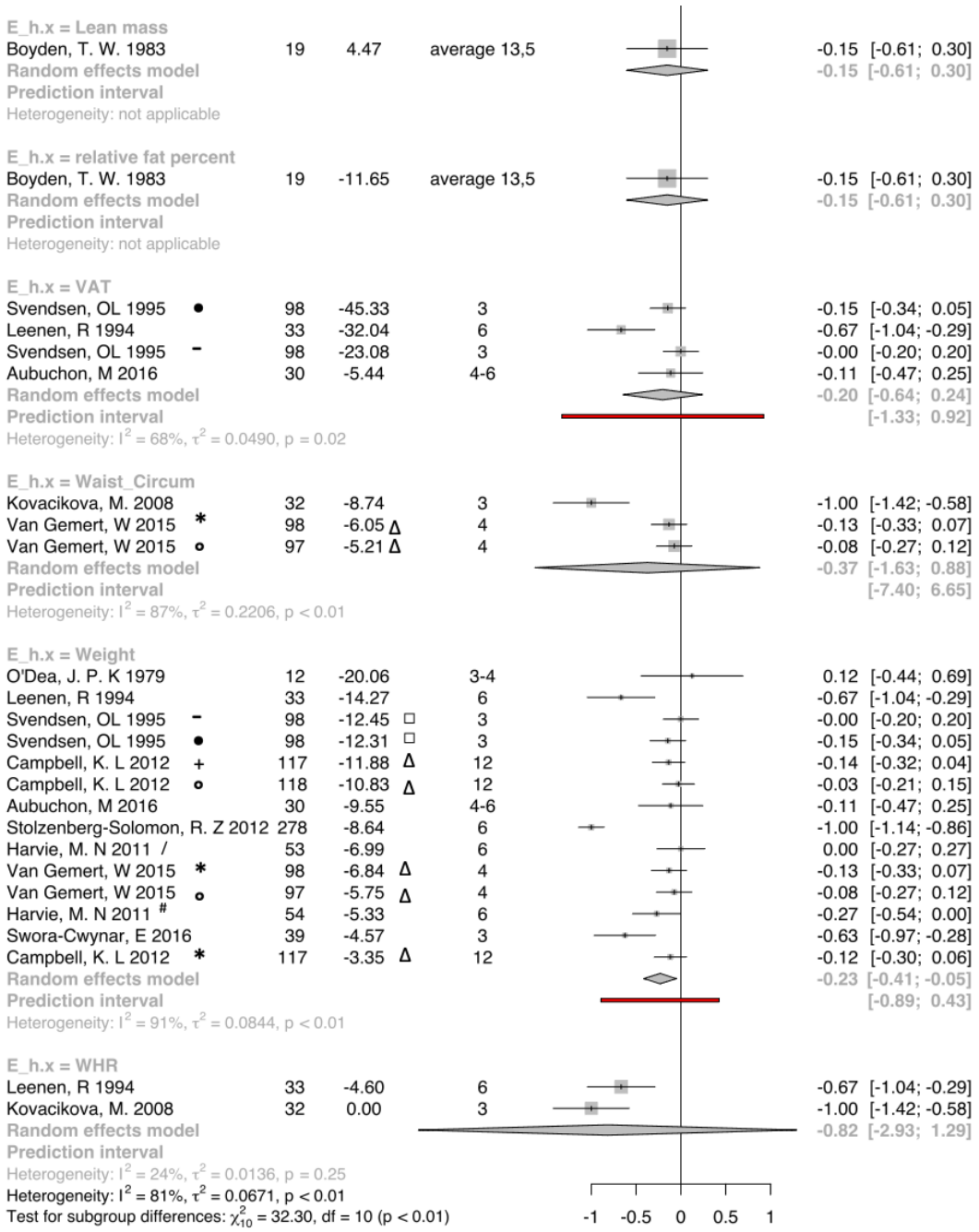


Figure 4.12.: Testosterone in lifestyle interventions. * exercise; ° diet; + exercisediet mixed; - android; • gynoid; Δ significant compared to control group; □ not mentioned if significant; # continuous energy restriction; / intermittent continuous energy; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

The overall SMD is -0.13 (-0.23;-0.02) and statistically significant. All studies individually show a negative SMD, except for Harvie et al. (2011) (intermittent continuous energy restriction group) which SMD is 0.00. The SMDs of the individual studies seem to be mostly in line, which can also be seen in the I^2 of 30% and τ^2 of <0.0001. Swora-Cwynar et al. (2016) was defined as an outlier, results without Swora-Cwynar et al. (2016) would change the SMD to -0.10 (-0.16;-0.04) and reduce the I^2 to 0.00% and the τ^2 to 0.00. The analysis for fat mass includes 10 studies. The overall SMD of -0.27 (-0.50;-0.05) is statistically significant. Harvie et al. (2011) (intermittent continuous energy group) and Svendsen et al. (1995) (gynoid group) display a SMD of 0.00, the other studies show a negative SMD. The results of the heterogeneity analysis show an I^2 of 73% and τ^2 of 0.07. When Kovacikova et al. (2008), which was defined as an outlier, was removed from the analysis, the SMD increased to -0.20 (-0.37;-0.02)and the I^2 and τ^2 decreased to 58.4% and 0.03. The analysis for weight includes 14 studies. The results show a significant overall SMD of -0.23 (-0.41;-0.05), an I^2 of 91% and a τ^2 of 0.08. Stolzenberg-Solomon et al. (2012) was defined as an outlier, analysis without this study would result in a SMD of -0.14 (-0.24;-0.03) and decreased I^2 of 44.7% and τ^2 of 0.004.

In the subgroup analysis of VAT 4 studies are included. The overall SMD is -0.20 (-0.64;0.24) which still shows a negative value but is not significant. The heterogeneity analysis shows an i2 of 68% and τ^2 of 0.05. 3 studies are included in the subgroup analysis for waist circumference. The overall SMD of -0.37 (-1.63;0.88) is not significant. The heterogeneity is high, with an I^2 of 87% and τ^2 of 0.22.
Even though most included studies have a negative SMD and all studies report a decrease in all types of anthropometric measures, only 4 studies showed a significant association between decrease in anthropometric data and decrease in testosterone. The other studies report no association. The results of our analysis show a significant association between decrease in BMI, percent body fat, fat mass or weight and decrease in testosterone.

Narrative summary

We also identified studies that were not possible to include in the analysis. The study of Sarwer et al. (2014), included in the narrative summary because it is the same study as Sarwer et al. (2018), investigated the effect of a surgical intervention on testosterone. The results of this study show an association between weight loss and decrease in testosterone. Kaaks et al. (2003) conducted a lifestyle intervention and found a positive association between decrease in BMI, WHR, WC or hip circumference and decrease in testosterone. This study was included was not amenable to meta-analyse because no measure of variance was reported. Monninkhof et al. (2009), included in the narrative summary because no measure of variance was reported, and McTiernan et al. (2004a), included in the narrative summary as only the group with a decrease of > 2 percent body fat was relevant for our study, also conducted a lifestyle intervention and these results show an association between decrease of > 2 percent body fat and decrease in testosterone. However, the lifestyle intervention studies of Friedenreich et al. (2010), which was included in narrative summary as only change of weight is reported, and Duggan et al. (2019), which was not amenable to meta-analyse as only the group with > 10 weight loss was relevant for our study, found no association between decrease in weight or weight loss of < 10 percent and change in

testosterone.

Summary

Surgical and lifestyle intervention types display similar results of the effect of body composition change on testosterone concentration. The results, as shown in Figure 4.11 and 4.12 show similar overall SMDs, which are negative for all subgroups. This indicates that in general, testosterone decreased between baseline and follow-up due to the intervention. In the surgical intervention group, the analysis of BMI shows an association between a decrease in BMI and decrease in testosterone. The analysis for weight change shows no association. In the lifestyle interventions an association was found between decrease in BMI, percent body fat, fat mass or weight and decrease in testosterone.

4.2.4. Free Testosterone

Surgical interventions

Figure 4.13 contains the change in free testosterone in surgical intervention studies. Only 4 intervention studies provided data. Three measured change in BMI and could therefore be meta analysed. The studies included in the BMI analysis all show a negative SMD and a significant overall SMD of -0.97 (-1.72;-0.21). The individual SMD values are similar across studies, which also shows in the I^2 of 25% and τ^2 of 0.03. This analysis shows an association between decrease in BMI through surgical intervention and decrease in free testosterone. The fourth study by (FRIEDMAN et al., 1982) is described in the narrative summary.

Lifestyle interventions

The change in free testosterone is displayed in Figure 4.14. BMI, percent body fat, fat mass, waist circumference and weight can be meta-analysed. A large overlap of the individual studies included in each analysis can be observed. The BMI analysis includes 4 studies and shows a negative overall SMD of -0.92 (-12.31;0.48) which is not significant. Since the SMDs of the individual studies range from -0.24 to -2.20, the between study heterogeneity is rather large with an I^2 of 92% and τ^2 of 0.70. The smallest overall SMD, -0.25 (-0.40;-0.10), was calculated in the percent body fat subgroup and is the only significant SMD. The heterogeneity is low, as I^2 = 35% and τ^2 = 0.001. The subgroup of fat mass is the only analysis that includes a study with a positive SMD, 0.23. Even though, the overall SMD of -0.62 (-1.48;0.25) is still negative, and the value is not significant. The I^2 of 90% and τ^2 of 0.60 indicate a high heterogeneity due to the big range between the individual SMDs (-2.20 to 0.23). The study of Kovacikova et al. (2008) was detected as an outlier in the fat mass group. The exclusion of this study would lead to an increase in SMD to -0.33 (-0.84;0.17), I^2 and τ^2 would decrease to 76.3% and 0.12. Also, the analysis of waist circumference and weight report a negative overall SMD, -0.90 (-3.58;1.77) and -0.68 (-1.47;0.11), which are not significant. The heterogeneity for these studies is rather high, for waist circumference the I^2 is 94% and τ^2 is 1.09, for weight the I^2 is 98% and τ^2 is 0.72. Stolzenberg-Solomon et al. (2012) was classified as an outlier in the analysis for weight. The

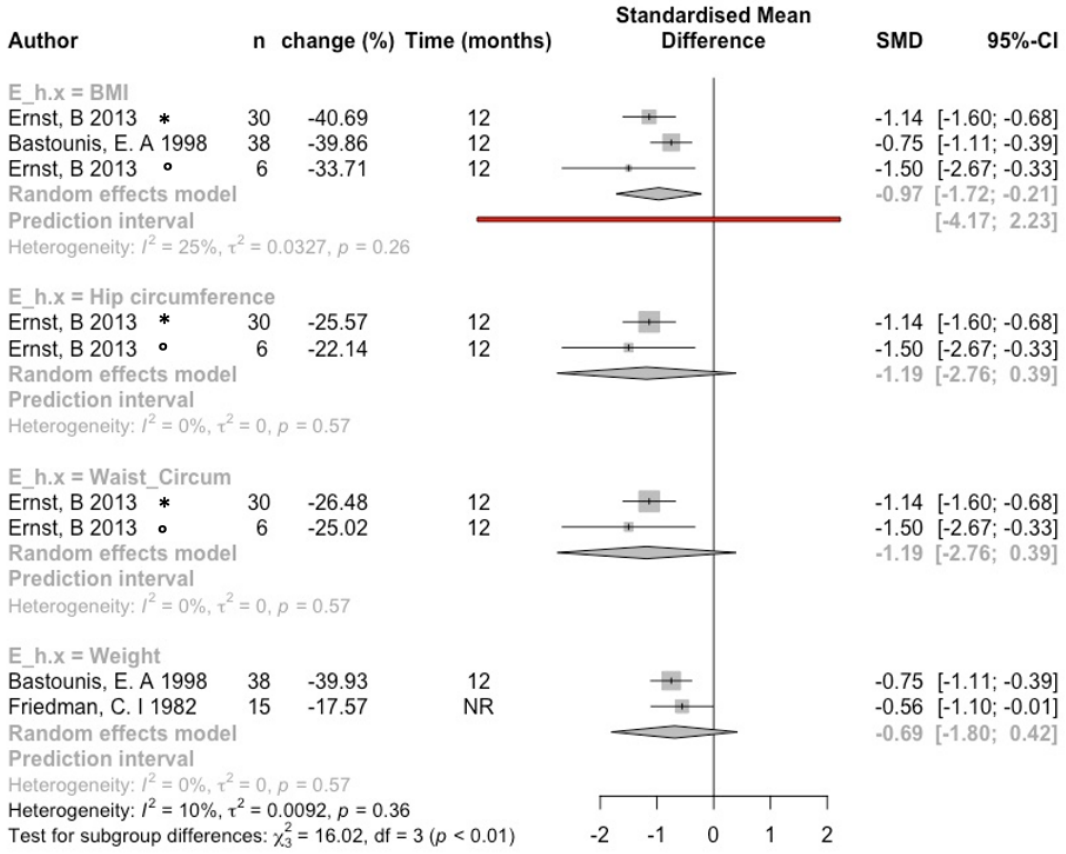
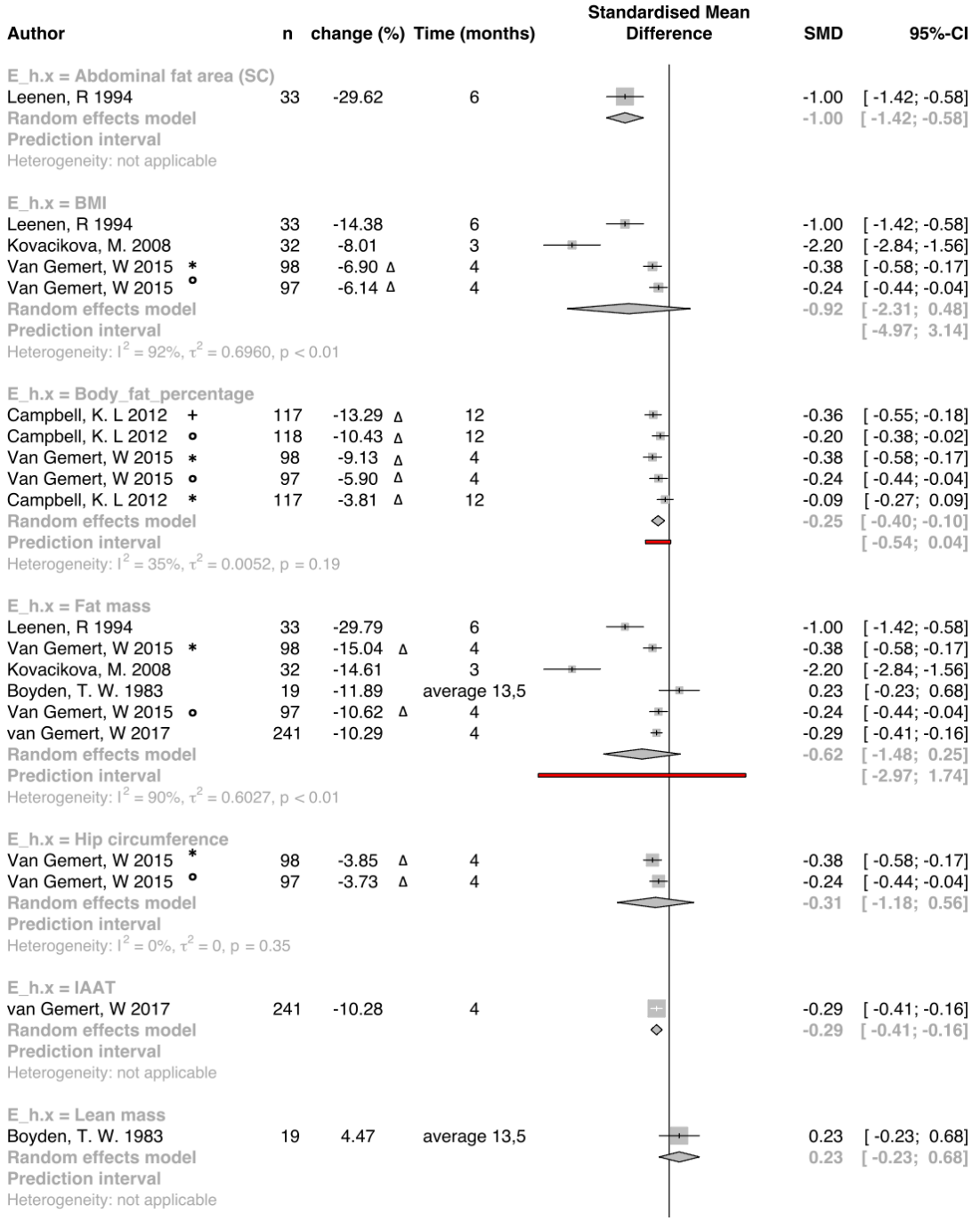


Figure 4.13.: Free Testosterone in surgical interventions. Duration not reported (NR) but a mean of 7.9 months until stable weight loss; * premenopausal women;° postmenopausal women; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed


Author
n
change (%)
Time (months)
Standardised Mean Difference
SMD
95%-CI
E_h.x = Abdominal fat area (SC)
Leenen, R 1994 33 -29.62 6 -1.00 [-1.42; -0.58]
Random effects model -1.00 [-1.42; -0.58]
Prediction interval
Heterogeneity: not applicable
E_h.x = BMI
Leenen, R 1994 33 -14.38 6 -1.00 [-1.42; -0.58]
Kovacikova, M. 2008 32 -8.01 3 -2.20 [-2.84; -1.56]
Van Gemert, W 2015 * 98 -6.90 Δ 4 -0.38 [-0.58; -0.17]
Van Gemert, W 2015 ° 97 -6.14 Δ 4 -0.24 [-0.44; -0.04]
Random effects model -0.92 [-2.31; 0.48]
Prediction interval [-4.97; 3.14]
Heterogeneity: I^2 = 92%, τ^2 = 0.6960, p < 0.01
E_h.x = Body_fat_percentage
Campbell, K. L 2012 + 117 -13.29 Δ 12 -0.36 [-0.55; -0.18]
Campbell, K. L 2012 ° 118 -10.43 Δ 12 -0.20 [-0.38; -0.02]
Van Gemert, W 2015 * 98 -9.13 Δ 4 -0.38 [-0.58; -0.17]
Van Gemert, W 2015 ° 97 -5.90 Δ 4 -0.24 [-0.44; -0.04]
Campbell, K. L 2012 * 117 -3.81 Δ 12 -0.09 [-0.27; 0.09]
Random effects model -0.25 [-0.40; -0.10]
Prediction interval [-0.54; 0.04]
Heterogeneity: I^2 = 35%, τ^2 = 0.0052, p = 0.19
E_h.x = Fat mass
Leenen, R 1994 33 -29.79 6 -1.00 [-1.42; -0.58]
Van Gemert, W 2015 * 98 -15.04 Δ 4 -0.38 [-0.58; -0.17]
Kovacikova, M. 2008 32 -14.61 3 -2.20 [-2.84; -1.56]
Boyden, T. W. 1983 19 -11.89 average 13,5 0.23 [-0.23; 0.68]
Van Gemert, W 2015 ° 97 -10.62 Δ 4 -0.24 [-0.44; -0.04]
van Gemert, W 2017 241 -10.29 4 -0.29 [-0.41; -0.16]
Random effects model -0.62 [-1.48; 0.25]
Prediction interval [-2.97; 1.74]
Heterogeneity: I^2 = 90%, τ^2 = 0.6027, p < 0.01
E_h.x = Hip circumference
Van Gemert, W 2015 * 98 -3.85 Δ 4 -0.38 [-0.58; -0.17]
Van Gemert, W 2015 ° 97 -3.73 Δ 4 -0.24 [-0.44; -0.04]
Random effects model -0.31 [-1.18; 0.56]
Prediction interval
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.35
E_h.x = IAAT
van Gemert, W 2017 241 -10.28 4 -0.29 [-0.41; -0.16]
Random effects model -0.29 [-0.41; -0.16]
Prediction interval
Heterogeneity: not applicable
E_h.x = Lean mass
Boyden, T. W. 1983 19 4.47 average 13,5 0.23 [-0.23; 0.68]
Random effects model 0.23 [-0.23; 0.68]
Prediction interval
Heterogeneity: not applicable

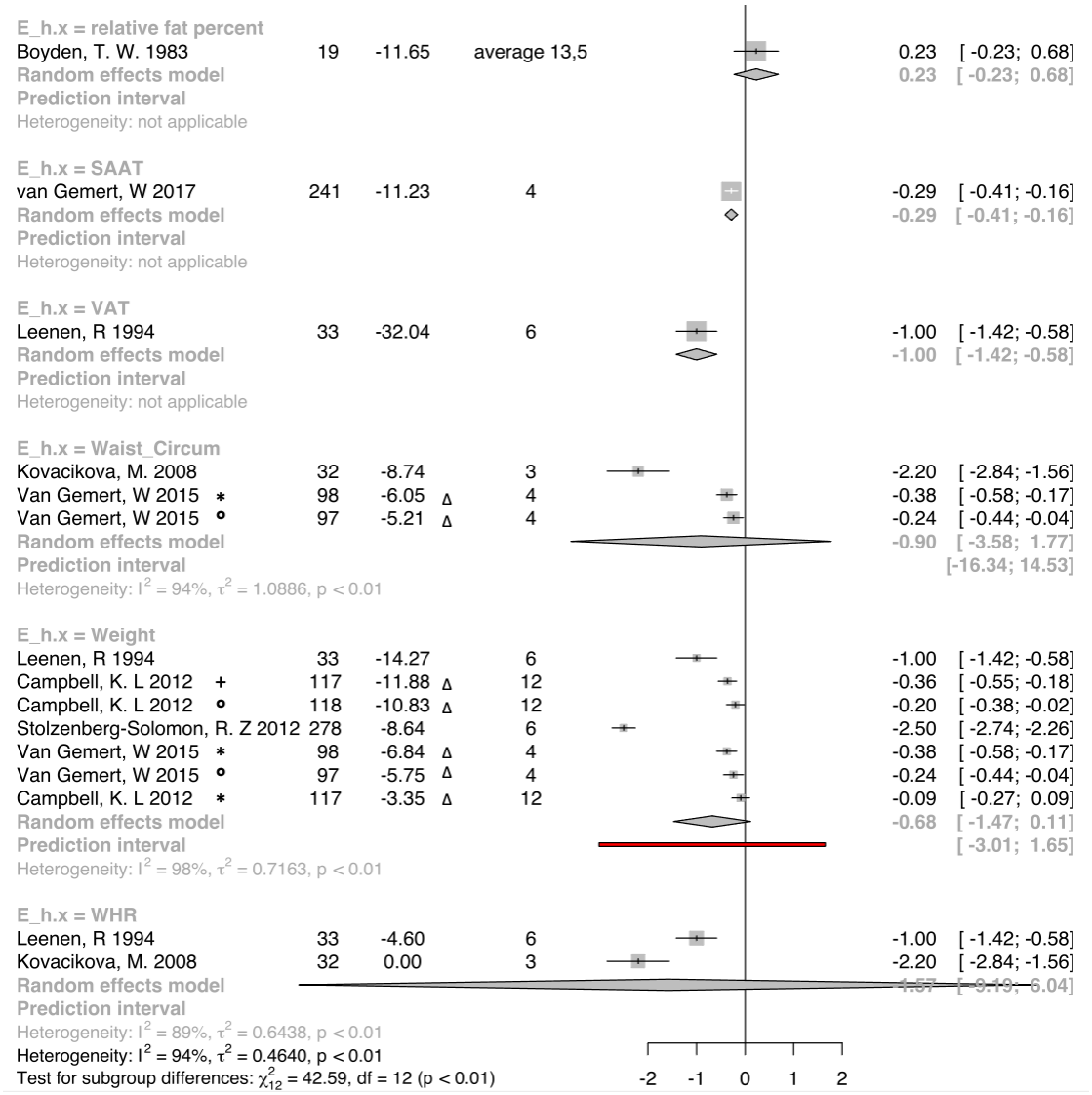


Figure 4.14.: Free testosterone in lifestyle interventions. * exercise; ° diet; + exercisediet mixed; Δ significant compared to control group; □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

results without this study showed an increased SMD of -0.33 (-0.62;-0.04), and a decreased I^2 of 72.3 % and τ^2 of 0.04.
Except for the study of Campbell et al. (2012) (exercise group) and Boyden et al. (1983), all studies report an association between decrease in body composition and decrease in free testosterone. These two studies show no association.

Narrative summary

Further studies, that were not amenable to meta-analyse, were identified. The study of FRIEDMAN et al. (1982), which could not be meta analysed as not enough similar studies were included, reports an association between weight loss and decrease in testosterone. The study by Kaaks et al. (2003), included in narrative summary because no measure of variance was reported, investigated the effect of a lifestyle intervention on free testosterone. The results show an association between decrease in BMI, WHR, WC or hip circumference and decrease in free testosterone. The result of the lifestyle interventions by Monninkhof et al. (2009), included in the narrative summary because no measure of variance was reported, and McTiernan et al. (2004a), not amenable to meta-analyse as only the group with a decrease of > 2 percent body fat was relevant for our study, also show an association between decrease of > 2 percent body fat and decrease in free testosterone. The lifestyle intervention of Duggan et al. (2019) came to a similar conclusion, as their results show a positive association between weight loss of > 10 percent and decrease in free testosterone. This study was included in narrative summary, as only the group with > 10 weight loss was relevant for our study. In comparison to that, the lifestyle intervention study of Friedenreich et al. (2010), included the in narrative summary as only change of weight is reported, did not find an association between decrease in weight and change in free testosterone.

Summary

Overall, the change in free testosterone of the individual studies from surgical and lifestyle intervention report similar results. The analysis for the individual anthropometric measurement analyses show a decrease in free testosterone with weight loss. However, not all were significant and therefore only decrease in BMI in surgical interventions and decrease in percent body fat and VAT in lifestyle interventions are associated with decrease in free testosterone.

4.2.5. Estradiol

Surgical interventions

Only 3 of the surgical intervention studies measured a change in estradiol, as displayed in Figure 4.15. Since a separate analysis has to be conducted for pre- and postmenopausal women, not enough studies were included in the individual subgroups, and it was not possible to meta-analyse their findings. However, the 2 studies which investigated premenopausal women, showed a statical significant decrease of estradiol with reductions in BMI and weight. The study including pre- and postmenopausal women also showed a decrease in estradiol with a reduction in BMI, but this was not significant.

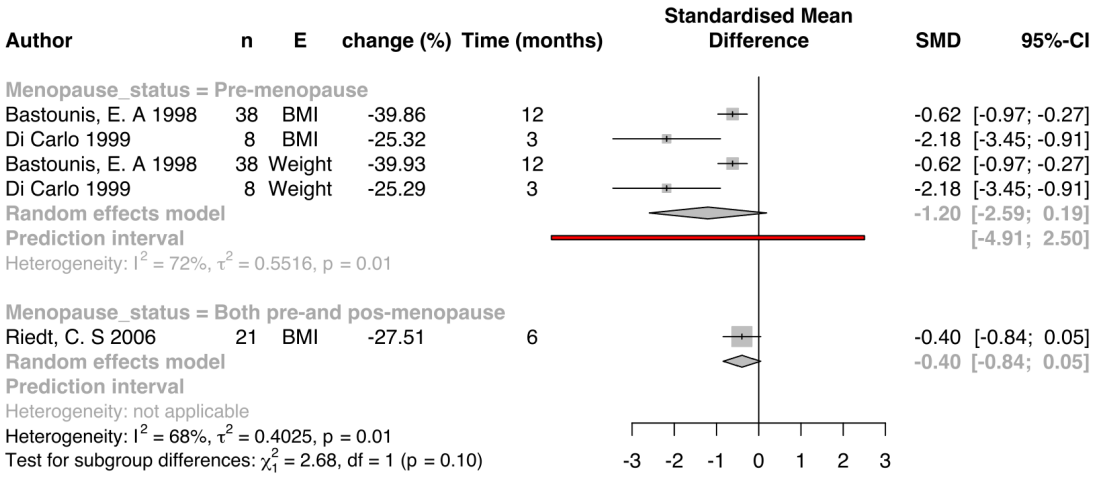


Figure 4.15.: Estradiol in surgical interventions. Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

Lifestyle interventions

The results for the change in estradiol are displayed in separate forest plots for pre- and postmenopausal women.
In the premenopausal group (Figure 4.16), fat mass (3 studies) was the only body composition measure that could be meta-analysed. The results report an overall SMD of -0.19 95% CI (-1.42; 1.04) but this change is not statistically significant. Two studies report a decrease in estradiol while only one of those reports a significant decrease, and one study reports a significant increase. A high heterogeneity between the studies can be seen, as I^2 is 85% and τ^2 is 0.21. Those results indicate no association between decrease in fat mass and change in estradiol in the studies evaluated in premenopausal women.
The analysis of estradiol change in postmenopausal women includes considerably more studies (Figure 4.17. Analyses were conducted for BMI, percent body fat, fat mass, hip- and waist circumference, and weight. The analyses of BMI includes 3 studies and shows an overall SMD of -0.12 (-0.48; 0.23), which is not statistically significant. The results for I^2 and τ^2 are 75% and 0.02. The analysis for percent body fat includes 5 studies. The overall SMD of -0.27 (-0.45; -0.10) is statistically significant. A moderate heterogeneity between the studies can be observed, as I^2 is 53% and τ^2 is 0.01. The analysis for fat mass includes 4 studies and reports an overall SMD of -0.11 (-0.32; 0.10). However, this change is not significant. Also for the analysis of fat mass a moderate heterogeneity can be observed with I^2 of 42% and τ^2 of 0.01. The analysis for hip and waist circumference included the same 3 studies, therefore, they report the same results. The overall SMDs of -0.12 (-0.48; 0.23) are not significant. For both subgroups I^2 is 75% and the τ^2 is 0.02. The analysis of weight and includes 9 studies. The result show a negative overall SMD of -0.62 CI (-1.44; 0.19), but it was not significant. The between study heterogeneity for the included studies is rather high, with an I^2 of 98% and τ^2 of 1.10. This is most likely caused by the study of Stolzenberg-Solomon et al. (2012) and O'dea et al. (1979) which SMDs differ

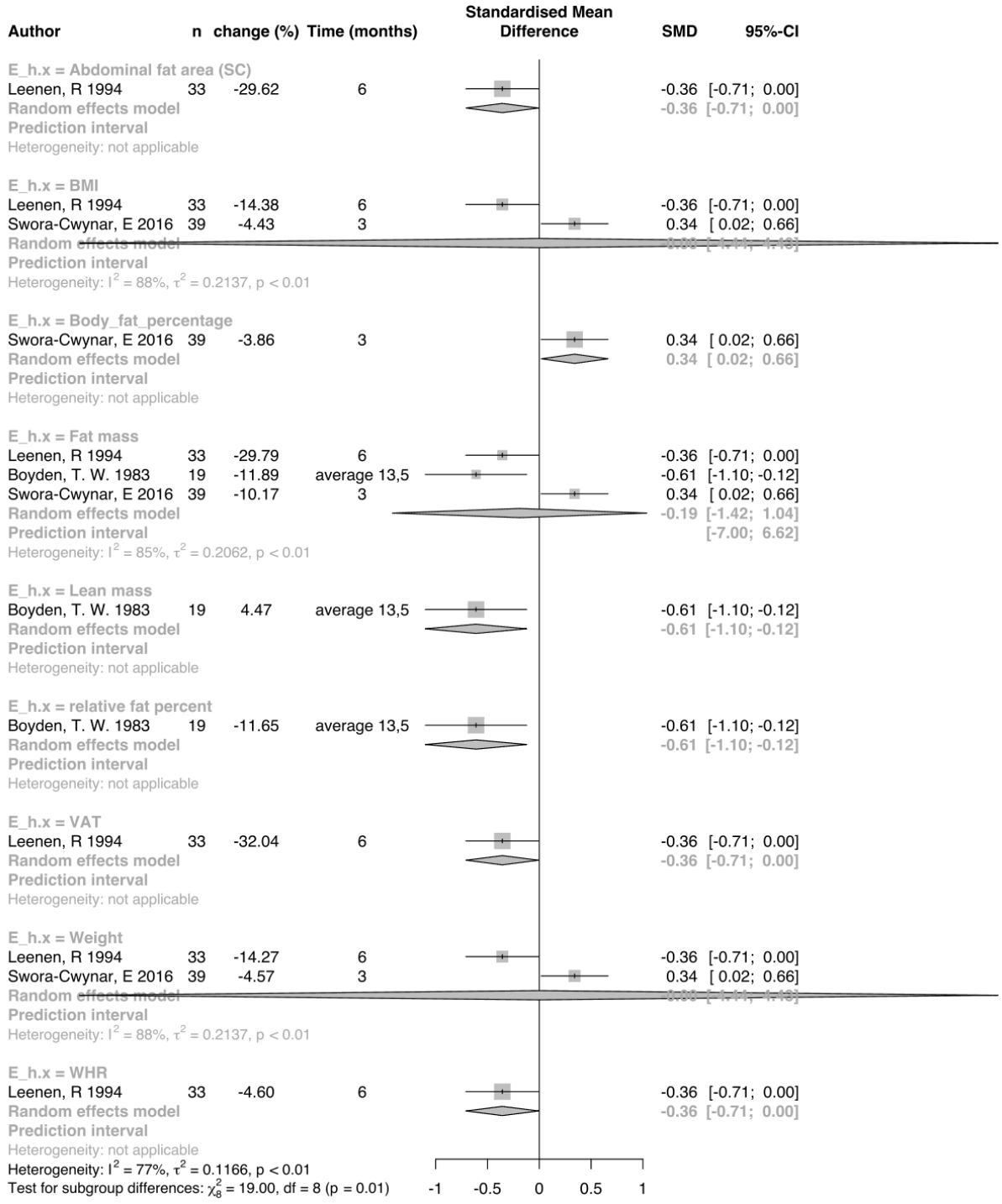


Figure 4.16.: Estradiol premenopausal women (lifestyle interventions). Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

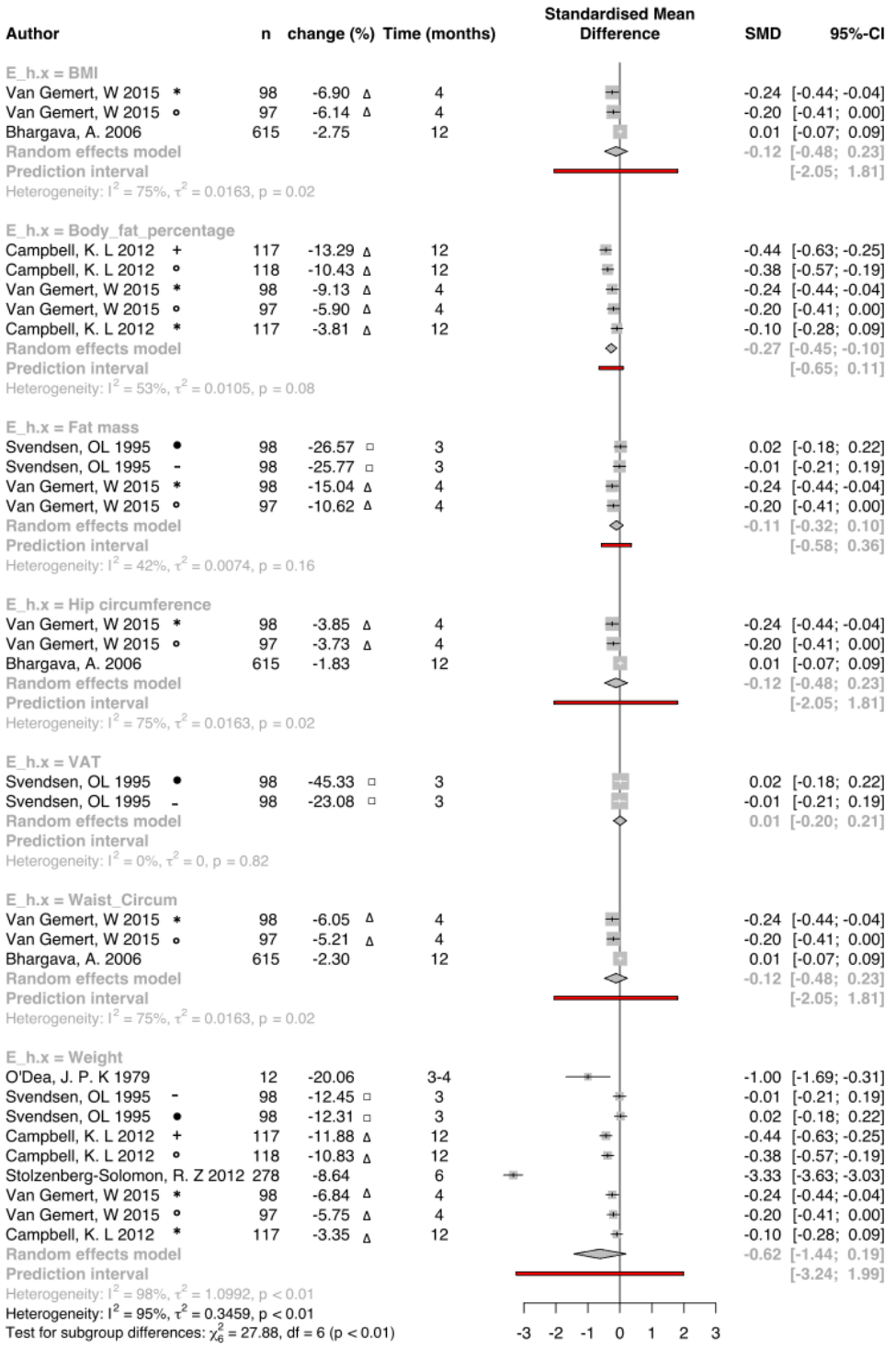


Figure 4.17.: Estradiol postmenopausal women in lifestyle interventions. * exercise; ° diet; + exercisediet mixed; - android; • gynoid; Δ significant compared to control group; □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

from the others. Stolzenberg-Solomon et al. (2012) is an outlier in the subgroup for weight. The results without the study resulted in a SMD of -0.22 (-0.41; -0.03) and reduced the amount of between study heterogeneity to I^2 of 71.5 and τ^2 of 0.03.

Narrative summary

We identified surgical and lifestyle interventions measuring estradiol that were not possible to include in the analysis. The study of Guney et al. (2003) investigated a surgical and lifestyle intervention in premenopausal women and was included in the narrative summary as the BMI change includes men and women, but estradiol was measured only in women. In the surgical intervention group, they found an association between decrease in BMI and decrease in estradiol. In the lifestyle intervention group, no association was found. Sarwer et al. (2014), included in the narrative summary because it is the same study as Sarwer et al. (2018), also investigated the effect of a surgical intervention on estradiol, but did not report information on the menopausal status of the participants. The results of their study show an association between weight loss and decrease in estradiol. This result was also found by Friedenreich et al. (2010) a lifestyle intervention study conducted in postmenopausal women. This study was not amenable to meta-analyse as only change of weight was reported. An association between decrease of > 2 percent body fat and decrease in estradiol in postmenopausal women as a result of lifestyle intervention was found by McTiernan et al. (2004b), which was not amenable to meta-analyse as only the group with a decrease of > 2 percent body fat was relevant for our study. The results of the surgical intervention study of (Beiglböck et al., 2020), indicate an association between decrease in BMI and increase in estradiol, but for this study no information on the menopausal status was provided.

However, the lifestyle intervention of Monninkhof et al. (2009) in postmenopausal women found no association between decrease of > 2 percent body fat and change in estradiol. Kaaks et al. (2003) also conducted a lifestyle intervention in postmenopausal women which also did not show an association between decrease in BMI, WHR, WC or hip circumference and change in estradiol. These two studies were included in narrative summary because no measure of variance (e.g. SD) were reported. Similar results were found by the lifestyle intervention study of, Duggan et al. (2019) as no association between weight loss of > 10 percent and estradiol in postmenopausal women could be observed. Duggan et al. (2019) was included in narrative summary, as only the group with > 10 weight loss was relevant for our study. The surgical intervention study of Sarwer et al. (2018) also found no association between weight loss and change in estradiol, but no information regarding the menopausal status was provided.

Summary

Overall, most studies in pre- and postmenopausal women report a decrease in estradiol after decrease in body composition achieved by lifestyle or surgical interventions. However, only some of those reductions are significant. The only association we found between decrease in any type of anthropometric parameter and change in estradiol was an association between decrease in percent body fat and decrease in estradiol in postmenopausal women. To reach a conclusion for

surgical interventions, further studies are necessary.

4.2.6. Free Estradiol

Surgical interventions

We did not identify surgical interventions studies that measured the change in free estradiol in pre or postmenopausal women.

Lifestyle interventions

In the premenopausal group, only one study is included, so we could not meta-analyse the estradiol for this group. However, this study shows a significant decrease in estradiol.

For the postmenopausal group, free estradiol change is displayed in Figure 4.18. The analysis of percent body fat (5 studies) and fat mass (3 studies) both show a significant negative overall SMD. For percent body fat, the overall SMD is -0.34 (-0.57; -0.10) with an I^2 of 73% and τ^2 of 0.03. The results of the analysis for fat mass show an overall SMD of -0.40 (-0.70; -0.10). For this analysis, the between study heterogeneity is low, with $I^2 = 46\%$ and $\tau^2 = 0.001$. The analysis for weight (6 studies) is the only analysis where the overall SMD of -0.94 (-2.52; 0.63) was not significant. The heterogeneity between the individual studies included in this subgroup is high, with $I^2 = 99\%$ and $\tau^2 = 2.22$. Stolzenberg-Solomon et al. (2012) was detected as an outlier in the subgroup of weight. When this study was removed from the analysis, the SMD changed to -0.34 95% CI (-0.57; -0.10) and the between study heterogeneity decreased to I^2 of 73.1% and τ^2 of 0.03, which is identical with the results from the percent body fat subgroup.

Narrative summary

Also for the free estradiol, studies were identified that could not be included in our meta-analysis. Kaaks et al. (2003), included in the narrative summary as no measure of variance was reported, conducted a lifestyle intervention in postmenopausal women and found an association between decrease in BMI, WHR, WC or hip circumference and decrease in free estradiol. This association was also found for weight in the lifestyle intervention study of Friedenreich et al. (2010), for weight loss > 10 percent in the lifestyle intervention of Duggan et al. (2019) and for percent body fat loss >2 percent in the lifestyle intervention of McTiernan et al. (2004b). Friedenreich et al. (2010) was only included in narrative summary because only change of weight is reported, Duggan et al. (2019) and McTiernan et al. (2004b) because only the group with a decrease of > 10 weight and decrease of > 2 percent body fat was relevant for our study. Monninkhof et al. (2009) conducted a lifestyle intervention in postmenopausal women and found no association between decrease of > 2 percent body fat and change in free estradiol. This study was not included in the meta-analysis as no measure of variance was reported.

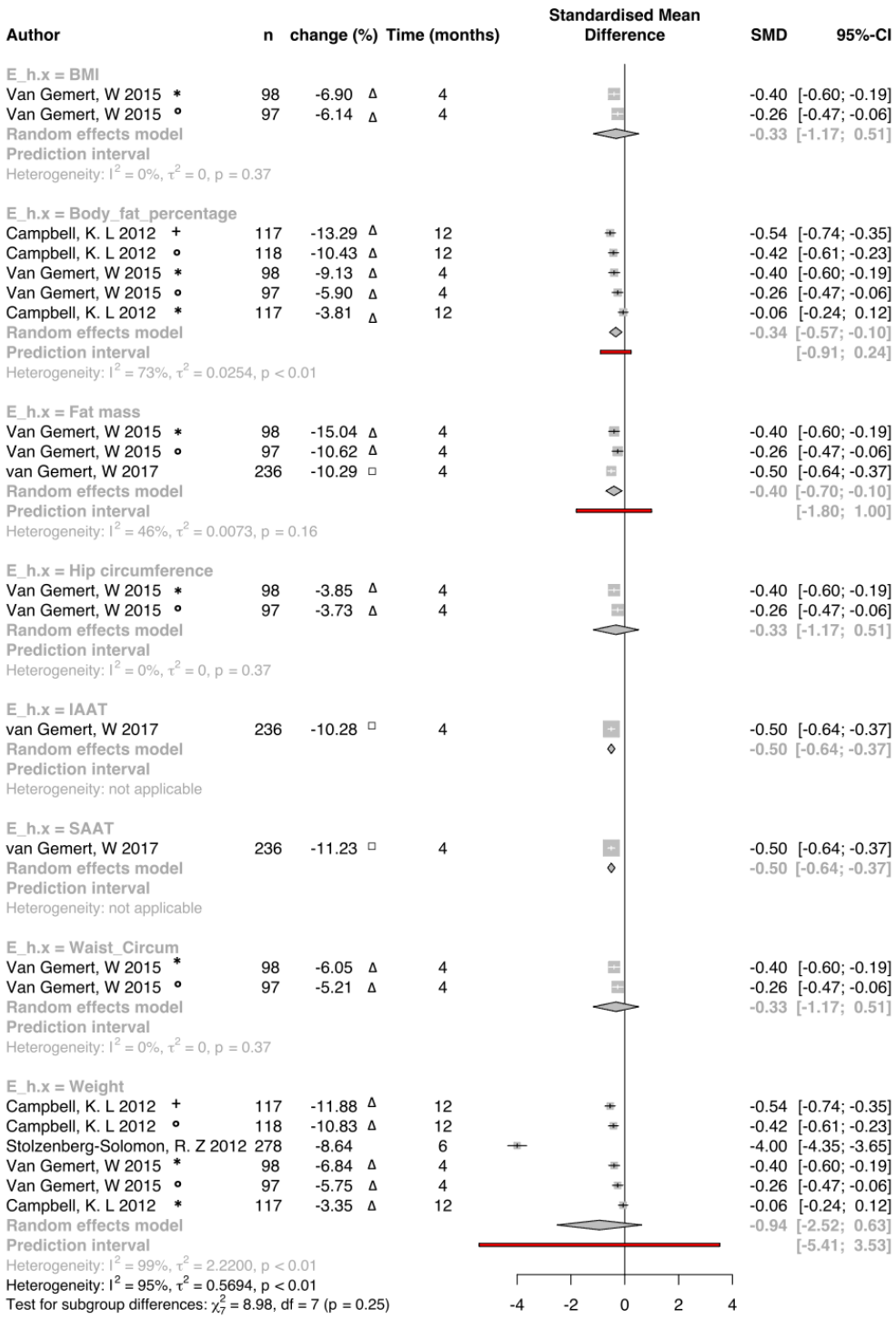


Figure 4.18.: Free estradiol in postmenopausal women in lifestyle interventions. * exercise; ° diet; + exercisediet mixed; Δ significant compared to control group; □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

Summary

The only associations that were found between decrease in type of anthropometric parameter and decrease in free estradiol were in postmenopausal women undergoing lifestyle interventions. More specifically, an association was found between decrease in percent body mass/fat mass and decreased in free estradiol. The other subgroups in the pre and postmenopausal plots did not include enough studies to meta-analyse the findings.

4.2.7. Estrone

Surgical interventions

We did not identify surgical interventions studies that measured the change in estrone in pre or postmenopausal women.

Lifestyle interventions

To investigate estrone change through lifestyle interventions, we also conducted separate analysis for pre- and postmenopausal women. Only 2 studies, that were amenable to meta-analyse and investigated premenopausal women were identified. Thus, it was not possible to analyse those (Figure 4.19) studies. However, Boyden et al. (1983) showed a statistical significant decrease and Leenen et al. (1994) reports a not significant decrease in estrone with a decrease in body composition.

The studies on postmenopausal women were amenable to meta-analyse, including studies on change in percent body fat, fat mass and weight shown in Figure 4.20. The analysis for percent body fat includes 5 studies and reports a significant overall SMD of -0.16 (-0.28; -0.04). No heterogeneity between the studies was found, which is indicated by I^2 of 0% and τ^2 of 0. Three studies are included in the analysis for fat mass. These results also show a negative overall SMD of -0.05 (-0.21; 0.10), but this change is not statistically significant. Similar to the percent body fat, no between heterogeneity was found for this analysis. The third analysis is for weight (6 studies) and shows a negative but not significant overall SMD of -0.46 (-1.26; 0.33). The results for this subgroup also show a high between study heterogeneity with I^2 of 98% and τ^2 of 0.56. The study by Stolzenberg-Solomon et al. (2012) was detected as an outlier in the analysis on change in weight. The results without this study showed an increased SMD of -0.16 95%CI (-0.28; -0.04) and the between study heterogeneity decreased to I^2 of 0.0% and τ^2 of 0, which is identical with the results from the percent body fat subgroup.

Narrative Summary

The studies by Monninkhof et al. (2009), not included in meta-analysis as no measure of variance was reported, and McTiernan et al. (2004b), not amenable to meat-analyse as only the group with a decrease of > 2 percent body fat was relevant for our study, both conducted a lifestyle intervention in postmenopausal women. The results of those studies show no association between

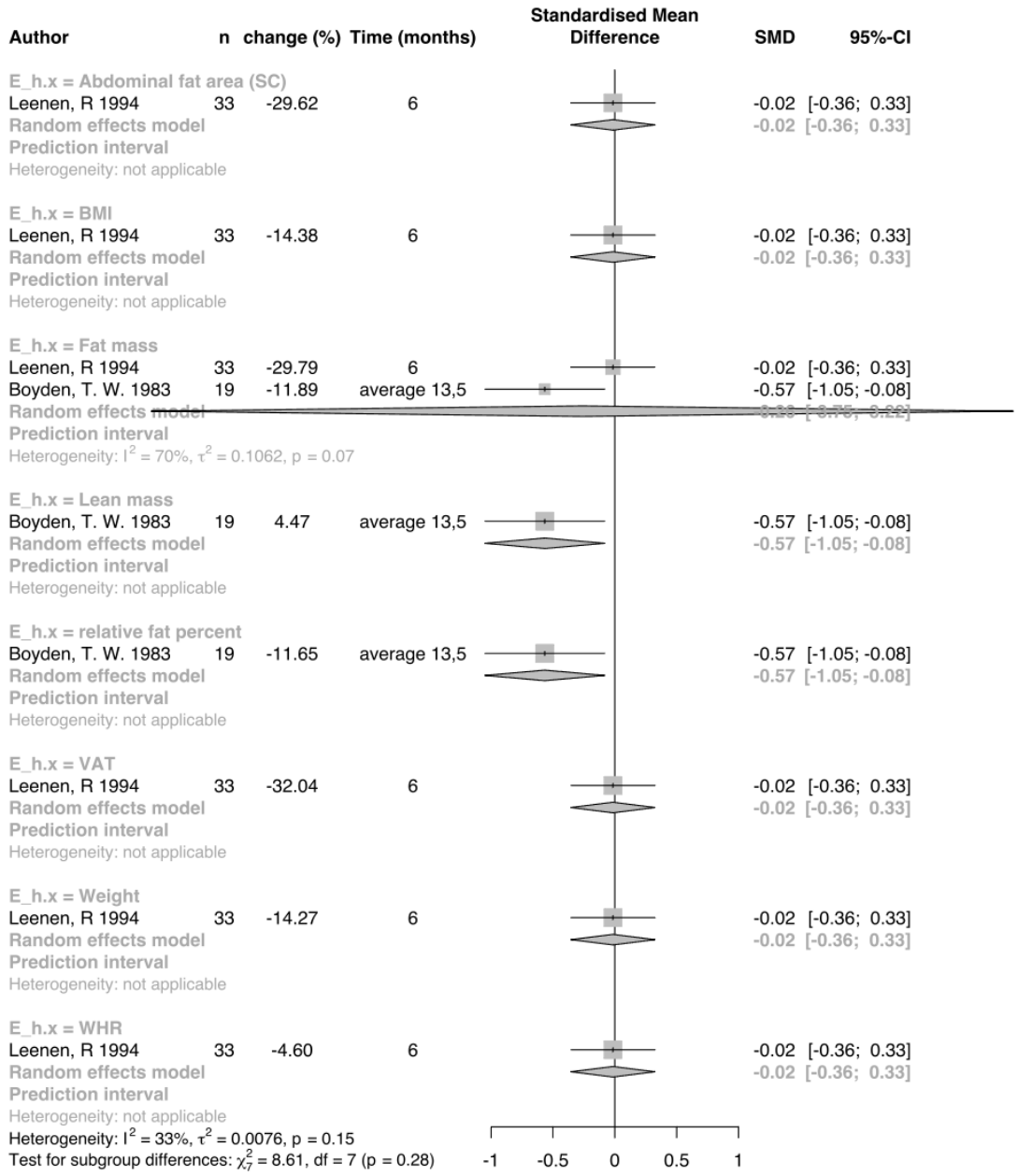


Figure 4.19.: Estrone in premenopausal women in lifestyle interventions. Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

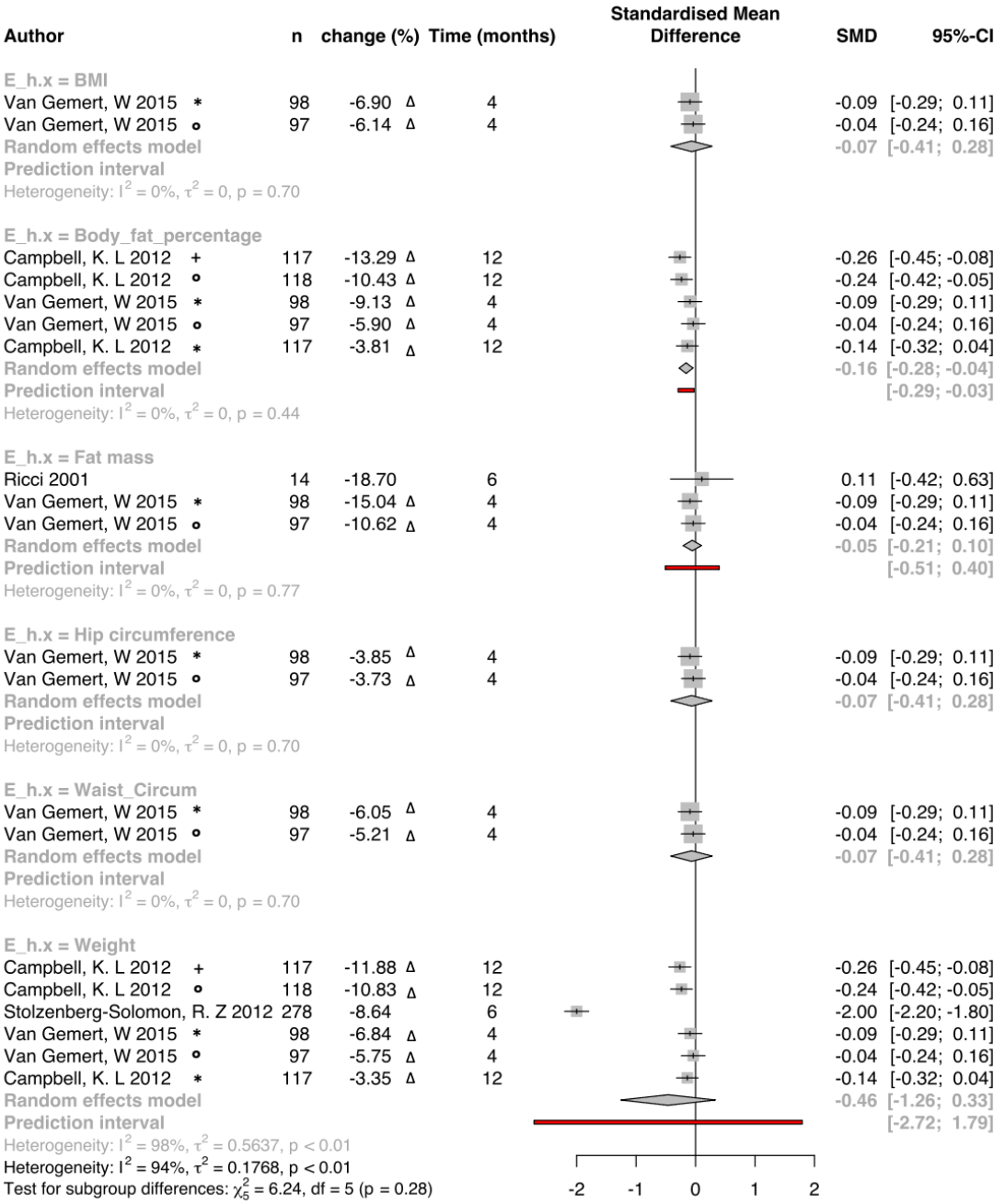


Figure 4.20.: Estrone in postmenopausal women in lifestyle interventions.* exercise; ° diet; + exercisediet mixed; Δ significant compared to control group; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

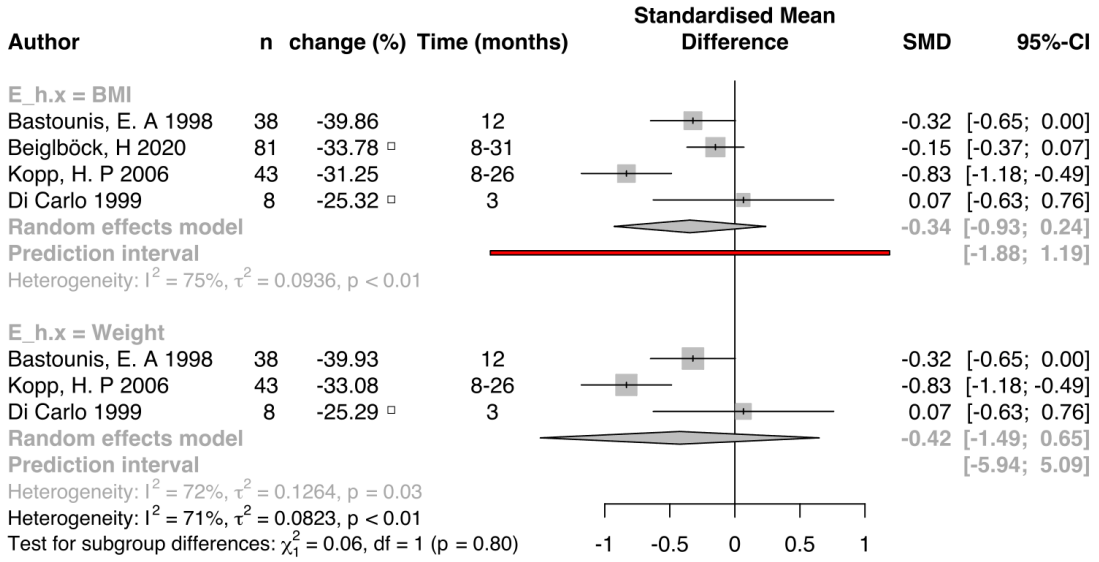


Figure 4.21.: Androstenedione in surgical interventions. □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

decrease of >2 percent body fat and change in estrone. Furthermore, the lifestyle intervention studies of Friedenreich et al. (2010) and Duggan et al. (2019) found no association between decrease in weight or weight loss of more than 10 percent and change in estrone. The study of Friedenreich et al. (2010) was not amenable to meta-analyse as only change of weight is reported and Duggan et al. (2019) because only the group with > 10 weight loss was relevant for our study.

Summary

The group of percent body fat in postmenopausal women undergoing lifestyle intervention is the only analysis that shows an association with estrone. More specifically, decrease in percent body fat was associated with a decrease in estrone. For the other subgroups included in the pre- and postmenopausal forest plots, there was not enough data to meta-analyse.

4.2.8. Androstendione

Surgical interventions

Figure 4.21 shows the change in androstenedione with surgical interventions. The analysis for BMI includes 4 studies and showed a negative overall SMD of -0.34 (-0.93; 0.24), however, this was not statistically significant. For this analysis I^2 is 75% and τ^2 0.09. The analysis for weight includes 3 studies and reports an overall SMD of -0.42 (-1.49; 0.65) which is also not significant. For this subgroup I^2 = 72% and τ^2 = 0.08.

Lifestyle interventions

The results for the analysis of change in androstenedione, in studies conducting lifestyle interventions, are displayed in Figure 4.22. Three anthropometric measurements were amenable to meta-analyse, including percent body fat, fat mass and weight. The analysis of the percent fat mass subgroup includes 7 studies and reports an overall SMD of -0.05 (-0.15; 0.06) and no heterogeneity between the included studies (I^2 = 9% and τ^2 = <0.0001). The analysis of fat mass shows similar results to those of the percent body fat analysis. Here, 6 studies are included and an overall SMD of -0.07 (-0.19; 0.05) was found. Also, no between study heterogeneity was observed (I^2 = 12% and τ^2 = <0.0001). The overall SMD of -0.08 95%CI (-0.17; -0.00) of the weight subgroup, including 10 studies, is in line with the findings from the other two subgroups. Again, no significant heterogeneity was found (I^2=39% and τ^2=0.001). None of the overall SMDs were statistically significant.

Narrative Summary

Additional studies, that were not amenable to meta-analyse, were identified. The study of Monninkhof et al. (2009) conducted a lifestyle intervention which found an association between decrease of > 2 percent body fat and decrease in androstenedione. This study is only included in narrative summary because no measure of variance was reported. Compared to these findings, the lifestyle intervention study of McTiernan et al. (2004a), not included in the meta-analysis because only the group with a decrease of > 2 percent body fat was relevant for our study, found no association between decrease of > 2 percent body fat and decrease in androstenedione. Furthermore, no association between decrease in weight and increase in androstenedione was found by the lifestyle intervention study by Friedenreich et al. (2010). This study is included in narrative summary because only the change of weight is reported.

Summary

In surgical intervention studies, no associations between decrease in weight or BMI and change in androstenedione were found. In the lifestyle interventions we also found no association between a decrease in percent body fat, fat mass or weight and change in androstenedione. The other types of body composition measure did not have enough studies to meta-analyse, and no clear associations were identified in the studies included in the narrative review.

4.2.9. No intervention studies

We also identified two studies, that met our inclusion criteria and reported weight change. However, this weight change was not a result of an intervention. We still found it informative to investigate the effect of this weight change on circulating sex steroid concentration. The longitudinal study by Goss et al. (2012) reported a significant increase in intra-abdominal adipose tissue (IAAT) between baseline and a follow-up duration of 2 years in postmenopausal women. The change in other body composition measurements was not significant. After 2 years, a statistical significant increase in SHBG and decrease in androstenedione was reported, the

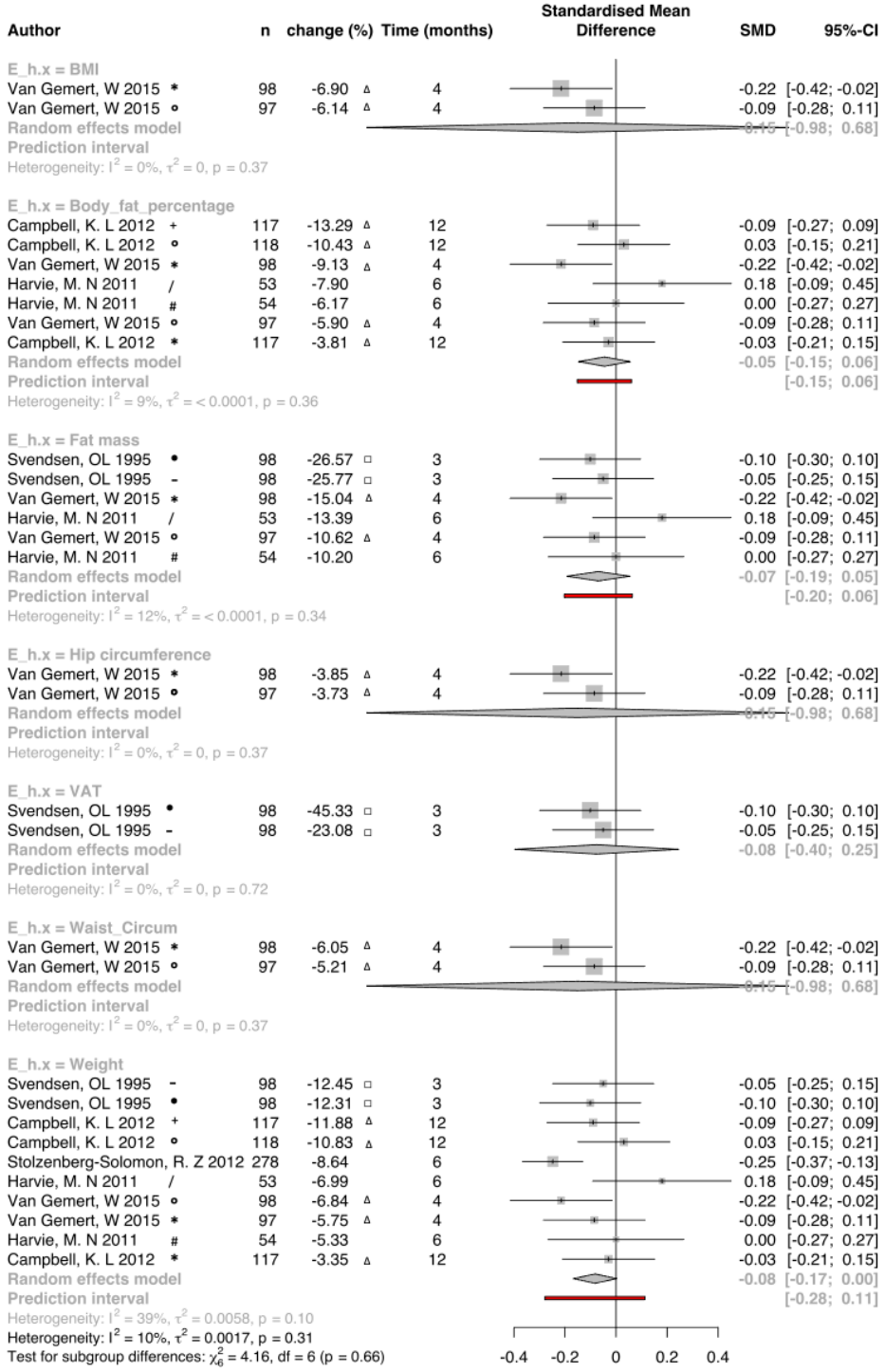


Figure 4.22.: Androstenedione in lifestyle interventions. * exercise; ° diet; + exercisediet mixed; - android; • gynoid; # continuous energy restriction; / intermittent continuous energy; Δ significant compared to control group; □ not mentioned if significant; Anthropometric measurements that only include 1-2 studies are included for illustration and were not meta-analysed

other measured sex steroids did not change significantly. But the analyses of change in body composition and sex steroids included women using hormone replacement therapy and non-users, and no separate analysis was conducted (Goss et al., 2012). The second study was a longitudinal study by Sowers et al. (2001) and investigated a duration of 3 years in premenopausal women. The results of this study show a significant increase in percent body fat, weight, and BMI and an increase in testosterone, however, it was not reported if testosterone change was significant (Sowers et al., 2001).

4.3. Risk of Bias

In this section, we present the result of the RoB assessment of the investigated studies. We include the individual assessments in Table A.2 which is presented in the appendix. As already discussed in the method section, the individual risk of bias questionnaires differed slightly between different study types. To grade the non-randomized intervention studies four categories (low, moderate, serious and crucial risk) were used. For all the other study types 3 categories (minimal, medium, and high risk) were used.

4.3.1. Non-randomized intervention studies

For the RoB of the non randomizes intervention studies, we assessed the overall grading according to the guidelines of the ROBINS-I tool (Sterne et al., 2016). Where if for example one domain out of 7 is graded as moderate, while all other domains are low, the overall judgement for the study is moderate. However, if one domain was classified as moderate the whole study did not automatically have to represent a moderate risk, but a low risk was also possible. Therefore, the judgment of the tool was not always in line with the overall judgment of the reviewer, and we assessed both the overall judgment of the tool plus the overall judgment of the reviewer for each study.

A total of 20 studies were non-randomized intervention studies. Using the overall judgment guidelines of the ROBINS-I tool (Sterne et al., 2016), 2 studies were at **low** risk, 15 studies at **moderate** risk, 3 studies at **serious** risk and 0 studies of crucial risk of bias. When overall judgment was made by the reviewer, 8 studies were at **low** risk, 10 studies at **moderate** risk, 2 studies at **serious** risk and 0 studies at **crucial** risk of bias.
This shows that compared to the guideline judgment, the reviewer judgment led to more studies graded as low instead of moderate. But, classification in the categories serious and critical does not differ substantially.
The reason, the studies were graded as “at **serious** risk of bias” was consistently due to high likelihood of uncontrolled confounding. However, the findings of those studies did not differ from the findings of others and, thus, these studies judged as serious risk of bias did not influence the overall summary estimates.

4.3.2. Randomized trials

As no guideline for the overall judgment of randomized trials exists, the judgement was made by the reviewer after completing the questionnaire. A total of 21 studies were evaluated. Out of those, 14 studies were at **minimal** risk, 4 at **medium** risk and 3 at **maximal** risk of bias. The reason, the studies were graded as "maximal risk of bias" was due to missing information (e.g., of compliance, missing data or drop-out rate). The results of two of the studies graded as "**maximal** risk of bias" did not differ from the results of others and therefore, they did not influence the overall summary estimate. The third study by Swora-Cwynar et al. (2016) was identified as an outlier in the analysis for testosterone and percent body fat. However, for the analyses of testosterone with other body composition measures as well as other sex steroids, it was not defined as an outlier and, thus, the results did not differ from other studies. Furthermore, when this study was removed from the analysis, the summary SMD did not change. Therefore, this study did not influence the overall summary estimate.

4.3.3. Cohort and cross-sectional studies

Also, for the cohort and cross-sectional studies, no guideline for the overall judgment exists. Therefore, the judgement was only done by the reviewer after completing the questionnaire. Only one studies was a cross-sectional study and was graded **medium** risk of bias. The only included cohort study was at **minimal** risk of bias.

5. Discussion

In this meta analysis, we analysed the associations between decrease in anthropometric data and change in sex steroids. At the beginning of each intervention, all studies reported a BMI ≥ 25 kg/m^2. In particular, we made the following observations:

- In surgical intervention studies, a decrease in **BMI** was significantly associated with a decrease in testosterone and free testosterone, and an increase in SHBG. In lifestyle interventions, it was significantly associated with decreased testosterone concentrations.
- **Weight** loss was significantly associated with an increase in SHBG in surgical interventions. In lifestyle interventions, it was significantly associated with a decrease in testosterone and increase in SHBG.
- For loss of **fat mass**, we could observe a significant association with a decrease in free estradiol (postmenopausal women), decrease in testosterone (pre and postmenopausal women) and increase in SHBG (pre and postmenopausal women) in the lifestyle interventions.
- Loss of **percent body fat** as a result of a lifestyle intervention was associated with a decrease in estradiol, free estradiol and estrone for post menopausal women and a decrease in testosterone, free testosterone and increase in SHBG for pre- and postmenopausal women.

For the other investigated sex steroids and types of anthropometric measures, either no association were found or not enough studies were identified to meta-analyse.

Possible biological associations between body composition and sex steroids. As described in section 2.3.1, testosterone, and estradiol can be formed in adipocytes. As reviewed by Calle and Kaaks (2004); Renehan et al. (2015), this formation is conducted with the help of two enzymes (aromatase and 7-hydroxysteroid dehydrogenase), which are produced by adipose tissue. This indicates that with higher levels of obesity and therefore higher amounts of adipose tissue, more testosterone and estradiol is formed (Calle and Kaaks, 2004). Another link between body composition and sex steroids is via insulin (Calle and Kaaks, 2004; Renehan et al., 2015). Obesity leads to increased insulin levels, which decreases SHBG, and results in higher levels of bioavailable estradiol and testosterone (Calle and Kaaks, 2004; Renehan et al., 2015). This link is particularly relevant for postmenopausal women, where the majority of estrogen production occurs in adipose tissue, whereas in premenopausal women estrogen is mainly produced by the ovaries (Simpson, 2003). As there seems to be a link between obesity and sex steroid concentration, we hypothesized that weight loss results in a change of sex steroid concentrations. Particularly, we hypothesized a decrease in testosterone and estradiol and increase in SHBG. Our findings show

that the concentration of some circulating sex steroids (testosterone, free testosterone, SHBG and postmenopausal estradiol, free estradiol and estrone) can be altered through weight loss as a result of surgical and/or lifestyle interventions. This shows that our findings are in line with this hypothesis.
For the adrenal androgens androstenedione and DHEAS our findings show no association with weight loss. However, their production is regulated through mechanistic pathways that may be independent of obesity (Antoniou-Tsigkos et al., 2019).

Associations between sex steroids and risk for breast, endometrial and ovarian cancer. As described in Section 2.3.1, increased testosterone and estradiol and decreased SHBG levels are likely to contribute to cancer development by increasing cell proliferation and decreasing apoptosis (Calle and Kaaks, 2004). Therefore, it is important to investigate associations between sex steroids and cancer. For **breast cancer** risk, associations have been described in pre- and postmenopausal women separately. Hormones, Endogenous and Breast Cancer Collaborative Group (2013) conducted a pooled analysis of seven studies including premenopausal women and found a positive association between the concentrations of testosterone, oestradiol, free oestradiol, oestrone, androstenedione, DHEAS and the risk of premenopausal breast cancer. For SHBG and progesterone, no association with risk of breast cancer was found (Hormones, Endogenous and Breast Cancer Collaborative Group, 2013). A review conducted by Brown and Hankinson (2015) came to a similar conclusion, as most studies reported a positive association between estradiol and premenopausal breast cancer risk. For postmenopausal women, Hormones, Endogenous and Breast Cancer Collaborative Group (2015) investigated data of a pooled analysis including 18 studies and found a strong positive association between estradiol, estrone and testosterone. In another review, Brown and Hankinson (2015) concluded that the available data supports a positive association between estradiol and breast cancer risk.

Associations between sex steroids and risk of **endometrial** cancer have also been investigated separately for pre- and postmenopausal women. The review by Brown and Hankinson (2015) stated that a positive association between circulating estrogen levels and postmenopausal endometrial cancer is consistently reported in studies to date. However, only 3 prospective studies were investigated. Allen et al. (2008) conducted a nested case-control study including 247 cases and 481 controls using serum blood. The results for postmenopausal women showed an association between increasing estradiol, free estradiol, estrone, testosterone, and free testosterone levels and endometrial cancer risk. SHBG showed a negative, and androstenedione and DHEAS showed no association with risk for endometrial cancer. No association was found between the concentration of sex steroids and endometrial cancer risk in premenopausal women. However, the authors state that the number of included participant was not sufficient for a conclusion (Allen et al., 2008).

For the association between sex steroids and **ovarian cancer** risk, fewer data than for breast cancer risk. A pooled analysis of 7 nested case-control studies by Ose et al. (2017) showed an association between a doubling of testosterone and a 25% increase in overall epithelial ovarian cancer risk, when top to bottom tertiles are compared. No association could be observed between free testosterone, androstenedione, DHEAS, and SHBG and overall epithelial ovarian cancer risk.

However, Ose et al. (2017) observed differences in androgens and SHBG and total epithelial ovarian cancer according to both menopausal status at blood collection and age at diagnosis. For premenopausal women at blood collection, a positive association was observed between androstenedione and SHBG and ovarian cancer risk (Ose et al., 2017). Furthermore, Ose et al. (2017) investigated the cancer risk by histologic subtype (endometrioid, mucinous, serous or clear cell tumours). For higher testosterone levels, they found an association with higher risk of endometrioid and mucinous tumours, but not the other subtypes. For free testosterone and androstenedione they only report an association with higher risk of mucinous tumours. No association for the histologic subtypes was found for DHEAS and SHBG (Ose et al., 2017). A nested case-control study by Trabert et al. (2019) investigated a possible association between circulating androgens and ovarian cancer risk in postmenopausal women. Their results exhibit no association between androgens or androgen metabolite levels and overall ovarian cancer risk. When the histological subtypes of ovarian cancer (serous and non-serous ovarian cancer) were investigated, the results showed that increased androsterone-glucuronide or total glucuronide metabolites resulted in an increased risk for non-serous but not serous ovarian cancer (Trabert et al., 2019). An association between estrogens and risk for ovarian cancer was investigated in postmenopausal women by the nested case-control study of Trabert et al. (2016). The results show a positive association between estrone and risk for overall ovarian cancer. But, the odds ratio when comparing the 5th quintile to the 1st is not significant. No association between estradiol and overall ovarian cancer risk was observed (Trabert et al., 2016). In the review by Brown and Hankinson (2015) only one relevant study was identified, but those results indicate a positive association between circulating estradiol and ovarian cancer risk, as the ovarian cancer risk in women with the highest estradiol levels was three times compared to the risk of women with the lowest estradiol levels.

Associations between hormone-related risk factors and breast, endometrial and ovarian cancer. Beyond the sex steroid hormones themselves, there is evidence on hormone-related risk factors that provides indirect support for an association between sex steroids and breast, endometrial and ovarian cancers. For breast cancer, the associations are investigated separately for the estrogen receptor (ER) and progesterone receptor progesterone receptor (PR) status, ER+PR+ and ER-PR-. According to the results of a meta-analysis by Ma et al. (2006), the risk for both receptor types of breast cancer was reduced by higher age at menarche. The results of the meta-analysis by Ma et al. (2006) show, that the risk for ER+PR+ cancer was reduced by 11% for every birth, but no association with ER-PR- was found. The risk for both cancer receptor types was reduced by breastfeeding (Ma et al., 2006). The meta-analysis of 8 studies by Gong et al. (2015) found, that per 2 year delay in age at menarche, the endometrial cancer risk was reduced significantly by 4%. The results of a meta-analysis (18 studies) which investigating the age at menopause showed, that the relative risk for endometrial cancer was 1.89 (1.58–2.26) for the highest compared to the lowest age at menopause (Wu et al., 2019). Raglan et al. (2019) reported, that the risk for endometrial cancer is reduced by parity (relative risk of 0.66 (0.60–0.74)). For ovarian cancer, the results of a meta-analysis including 27 studies showed a relative risk of 0.85 (0.75–0.97) for ovarian cancer when comparing the highest age at menarche to the lowest (Gong et al., 2013). Also, the results of a meta-analysis conducted by Sung et al. (2016), reported an

association between first birth and breastfeeding (<6 months) and a significantly reduced risk for epithelial ovarian cancer.
The **association of exogenous hormones on cancer risk** is also of interest. Gierisch et al. (2013) report in a systematic review that oral contraceptive use increases breast cancer while endometrial cancer decreases, compared to never use. The study by Burchardt et al. (2022) showed that also modern formulations of oral contraceptive are associated with breast cancer risk, as they report an association between current use and higher risk of invasive breast cancer. For menopausal hormone therapy, the review by Collaborative Group on Hormonal Factors in Breast Cancer (2019) reported an association between higher breast cancer risk and use of menopausal hormone therapy (except for the menopausal hormone type vaginal estrogens). The risk for endometrial cancer is increased in women using hormone therapy (estrogen), compared to non-user (Grady et al., 1995). However, the study by Chlebowski et al. (2016) reported that hormone replacement therapy of estrogen and progestin combined reduces the incidence of endometrial cancer. Furthermore, evidence also exists for an association between hormone replacement therapy use and higher ovarian cancer risk (Zhou et al., 2008). The findings of these studies show, that not only endogenous, but also exogenous hormones and hormone-related risk factor influence cancer risk.

Contributions of this study:

- We systematically reviewed all the relevant data that has been published on the topic (to the best of our knowledge), and assessed the quality of the selected studies in a methodic way.
- We meta-analysed the findings of relevant studies (separately for surgical and lifestyle interventions) and identify associations and patterns.
- Our work helps to clarify the underlying mechanisms through which weight loss may impact (lower) risk of endometrial, ovarian and breast cancer, and our findings provide further support for a potential benefit of weight loss with respect to a decreased risk of cancer.

Strengths of our approach are that we identified all current studies on the topic of weight loss interventions and circulating sex steroid concentration in women. We meta-analysed the data where possible and described other studies identified studies in a narrative way. Furthermore, we conducted separate analysis for pre- and postmenopausal women for sex steroids that are influenced by menopausal status.

Limitations of our approach are that only a small number of studies were included in certain analyses, in some cases only three studies. Also, some studies only included a small number of participants. Furthermore, we could observe a heterogenous change in weight loss between the studies, as weight loss ranges from 3.35% to 39.39%. Another limitation is the heterogeneity between the duration of intervention of the individual studies, as the shortest follow-up time was 3 months but the longes duration was 48 months for surgical and 13.5 months for lifestyle interventions.

Future directions: As the results of our meta-analysis indicate that the concentration of some circulating sex steroids can be altered by a weight loss intervention, additional research is necessary to conclude how the change in concentration achieved by weight loss affects the risk for endometrial-, ovarian- and postmenopausal breast cancer risk.
As not enough studies that measured progesterone, 16-alpha OHE-1, 2-OHE-1 and 2-OHE-1 to 16-alpha OHE-1 ratio were identified, it was not possible to conduct analysis for those sex steroids. Furthermore, not a sufficient number of studies measuring estradiol, free estradiol or estrone in premenopausal women could be identified for meta-analysis. However, it would be important to investigate a possible association between weight loss and progesterone, as well as estradiol, free estradiol and estrone in postmenopausal women in future research.
Subsequently, it may also be of relevance to investigate the association between sex hormones and breast cancer in men. Since the occurrence of this disease is relatively rare, there is currently little data on the possible association between sex hormone concentration and breast cancer. Brinton et al. (2015) shows in a nested-case control study that compared to androgens, estradiol levels were associated with breast cancer risk in men.
For a better understanding of the link between obesity and endometrial-, ovarian- and postmenopausal breast cancer risk, it is necessary to investigate other biological mechanisms that are likely to play a role. Apart from sex steroids, also insulin and Insulin-like growth factor-I, as well as inflammation are promising pathways, since they are related pathways. For these mechanisms, evidence for an association with adiposity and endometrial-, ovarian- and postmenopausal breast cancer risk exists. Individual studies reported an association between endometrial- ((Dossus et al., 2010), (Wang et al., 2011)), ovarian- ((Clendenen et al., 2011)) and postmenopausal breast cancer ((Agnoli et al., 2017))and circulating inflammation markers such as Interleukin 6, Interleukin 1 receptor antagonist and C-reactive protein. For circulating insulin and IGF, studies reported an association with breast cancer in pre- but not postmenopausal women ((Hankinson et al., 1998)) and in ovarian cancer ((Li et al., 2016)). In the larger systematic review project, that our work is a part of, the role of insulin and IGF, and inflammation will be investigated in detail in future reviews.

Conclusion: In the studies included in our analysis, a weight loss caused by surgical or lifestyle intervention led to a significant reduction in testosterone and estradiol (postmenopausal women) and increase in SHBG. Therefore, our findings imply that weight loss achieved through an intervention causes a decrease in those sex steroids, thus providing support for decreases in sex steroid hormone concentrations as a mechanism linking weight loss to reduced risk of hormone-related cancers. Our work shows positive effects that come with weight reduction in overweight and obese people, and the importance of preventing.

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Acronyms

16-alpha OHE-1 16-alpha-hydroxyestrone. 11, 67

2-OHE-1 2-Hydroxyestrone. 11, 67

BMI Body mass index. v, 3–6

CI confidence interval. 4, 15

DHEA dehydroepiandrosterone. 11

DHEAS dehydroepiandrosterone-sulfate. 21

DHT Dihydroesterone. 11

ER estrogen receptor. 65

HC hip circumference. 3

HRT hormone replacement therapy. 12

hydroxyprogesterone 17-alpha-hydroxyprogesterone. 11

IAAT intra-abdominal adipose tissue. 58

IGF-I insulin-like growth factor-I. 1

LH Luteinizing hormone. 13

NAFLD Non-alcoholic fatty liver disease. 13

OC oral contraceptives. 12

PCOS Polycystic ovary syndrome. 13

PR progesterone receptor. 65

RoB Risk of Bias. 16

SD standard deviation. 14

SE standard error. 15

SHBG Sex hormone binding globulin. v

SMD standardized mean difference. 15

VAT visceral adipose tissue. 11

WC waist circumference. 3

WHR waist-to-hip ratio. 3

WHtR waist-to-height ratio. 3

A. Additional summary tables

Author	Menopausal status	Study Design	Intervention type	Follow-up duration (in months)	Sample description	Study sample size
Di Carlo et al. (1999)	Pre	NRI	SI	3	Severely obese women in whom amenorrhea developed after the procedure; Age: 26,9 (SD= 5,3)	8
Mingrone et al. (2002)	Pre	RCT	DI / SI	12	Obese women; Age: 30-45	surgical=21, diet=31
Guney et al. (2003)	Pre	NRI	DI / SI	12	Morbidly obese, BMI >=40 kg/m2, Age (women for surgical int): 33,2 (SD=7,7), Age (women for diet int): 39,9 (SD=2,7)	surgical=14, diet=53
Savastano et al. (2005)	Pre	NRI	SI	24	Healthy but morbid obese women; Age: 36,7 (SD=6,4)	30
Kopp et al. (2006)	Pre	NRI	SI	8-26	Severly obese women ; Age: 41 (SD=7)	43
Riedt et al. (2006)	Pre & post	NRI	SI	6	Obese and extremly obese women; Age: 43,9 (SD=10,4)	21
Ernst et al. (2013)	Pre & post	NRI	SI	12	Severly obese women ; Age: 41,2 (SD=9,6)	pre=30, post=6
Sarwer et al. (2014)	NR	NRI	SI	24	-	102

Sarwer et al. (2018)	NR	NRI	SI	48	Obese women who met to undergo bariatric surgery ; Age: 25-60	106
Paul et al. (2020)	Pre	NRI	SI	12	Healthy women; Age: media = 37 (range= 20-48)	68
Beiglböck et al. (2020)	NR	NRI	SI	19.3 ± 11.5 months	Healthy, Age: 40 (SD= 11)	81
Bastounis et al. (1998)	Pre	NRI	SI	12	Morbidly obese patients, Age: 34,3 (SD=5,9)	38
Linkov et al. (2017)	NR	NRI	SI	6	Female bariatric surgery patients with BMI 35, Age: 43,88 (SD=11,66)	107
Goodfriend et al. (1999)	Pre	NRI	DI	4	Women with BMI>=30 kg/m2, Age: 73 (SD=1)	21
Van Rossum et al. (2000)	Post	NRI	DI	6	Obese, Age: not repoted	54
Ricci et al. (2001)	Post	RCT	DI	6	Obese women; Age: 55,0 (SD=8,0)	14
Kaaks et al. (2003)	Post	RCT	DI	5	healthy women, Age:58 (rang= 50-65)	50
Bhargava (2006)	Post	RCT	DI	12	Healthy, Age: 60,63 (SD= 6,63)	615
Kovacikova et al. (2008)	Pre	NRI	DI	3	overweight and obese women, Age: 42,1 (SD=1,9)	32
Harvie et al. (2011)	Pre	RCT	DI	6	normal or healthy, I	IER=53, CER=54
Campbell et al. (2012)	Post	RCT	DI / EI / DI + EI	12	, Age: 58,1 (SD=5)	Diet= 117, Exercise=118, Diet+Exercise=117

Monninkhof et al. (2009)	Post	RCT	EI	12	sedentary postmenopausal women, BMI>22kg/m^2, Age: 58,9 (SD=4,6)	96
van Gemert et al. (2015)	Post	RCT	DI / EI	4	Healthy women, Age: 50-59	Diet= 97, Exercise=98
Rock et al. (2016)	Pre & post	RCT	DI	12	Obese women, insulin sesntive, low_fat_group: Age = 50 (range=25-68), walnut_rich_group: Age =50 (range=22-67), low_carb_group: Age =50 (range=25-72),	lowfat=68, walnutrich=65, lowcarb=61
Swora-Cwynar et al. (2016)	Pre	RCT	DI	3	Obese women, Age: 31,2 (SD=8,3)	39
O'dea et al. (1979)	Post	NRI	DI	3-4	Obese women; Age: 50-63	12
Leenen et al. (1994)	Pre	NRI	DI	6	Healthy women, Age: 39 (SD=5)	33
Kraemer et al. (2003)	Pre	NRI	EI	9	college women tennis players,non_periodized= Age:18,6 (SD=1,3), periodized= Age:19,2 (SD=1,1)	non_periodized=10, periodized=9
Caballero and Maynar (1992)	Post	NRI	EI	4	Participants were at least one year post-menopausa, Age: 54 (SD=7)	18

McTiernan et al. (2004a)	Post	RCT	EI	12	Women (lost > 2% body fat) with BMI>=24 kg/m2, percent body fat>33Percent, Age: 60,7 (SD=6,7)	26
Campbell et al. (2007)	Pre	RCT	EI	3	Hospitalized, obese women, Age: 25,5 (SD=1,1)	17
Friedenreich et al. (2010)	Post	RCT	EI	12	postmenopausal for at least 24 months & healthy, Age: 61,2 (SD=5,4)	152
Kim and Kim (2012)	Post	RCT	EI	4	obese, no menstruation for at least one year and plasma FSH levels were higher than 30 mIU/mL, sedentary women, Age: 54,53 (SD=2,82)	15
Boyden et al. (1983)	Pre	NRI	EI	average 13,5	healthy, menstruating regularly, Age: 29,3 (SD=24 to 37)	19
McTiernan et al. (2004b)	Post	RCT	EI	12	sedentary women (lost > 2% body fat), BMI>=24 kg/m2, percent body fat>33Percent, Age: 60,7 (SD=6,7)	26
Sowers et al. (2001)	pre & peri	Cohort	NI	36	pre and perimenopausal women, Age: average 38 (Range= 25-45)	511
Goss et al. (2012)	Post	CS	NI	24	Healthy women, Age: 51,2 (SD=2,8)	18
Aubuchon et al. (2016)	Pre	RCT	DI / EI	4-6	women, non smokers Age: 40 (SD=5,9)	30

Van Gemert et al. (2017)	Post	CS	DI / EI	4	Overweight women, Age:60 (SD=4,8)	243
Duggan et al. (2019)	Post	RCT	DI / EI	30	healthy, overweight (BMI > 25 kg/m2), sedentary women, Age: 50 to 75 years	31 (group that lost >10% weight)
FRIEDMAN et al. (1982)	Pre	NRI	SI / DI	mean of 7.9 months until stable weight loss	morbidly obese, in excess of 50% over ideal body weight, Age: 35,2 (SD=7)	15
Svendsen et al. (1995)	Post	RCT	DI / EI	3	Healthy, overweight women, Age: (SD=)	n-estimated: gynoid = lowest tertiles of WHR, 98/3 -> n~32\nandroid = highest tertiles of WHR, 98/3 -> n~32
Stolzenberg-Solomon et al. (2012)	Post	RCT	DI / EI	6	Overweight/obese postmenopausal, Age: 59,3 (range= 46 - 78)	278

Table A.1.: Study description summary table. Non-randomized intervention study (NRI), randomized controlled trial (RCT), cross-sectional study (CS), exercise intervention (EI), diet intervention (DI), surgical intervention (SI), not reported (NR), standard deviation (SD), Body mass index (BMI), Waist hip ratio (WHR), intermittent continuous energy (IER), continuous energy restriction (CER)

Author	Body fatness measure	Outcome measure	Comments	Summary findings	ROB assesment
Di Carlo et al. (1999)	Weight (unit=kg), BMI (unit=kg/m^2)	Androstendione (unit = ng/ml, measure = RIA), Estradiol (unit = pg/ml, measure = RIA), Testosterone (unit = ng/ml, measure = RIA), DHEAS (unit = µg/dl, measure = RIA)	-	Weight, BMI: not reported if significant but seems like it ↓ ; Estradiol: ↓	moderate
Mingrone et al. (2002)	Fatmass (unit = kg, measure = DEXA), Weight (unit = kg), BMI (unit = kg/m^2)	SHBG (unit = nmol/l, measure = Immunoassay)	-	for surgical intervention = Fatmass, Weight, BMI: ↓ SHBG: ↑; for diet intervention = Weight: ↓	minimal
Guney et al. (2003)	BMI (unit=kg/m^2)	Estradiol (unit = pg/ml, measure = RIA)	Narrative summary: BMI change for men and women, Estradiol only for women	BMI: ↓, for surgery intervention = Estradiol: ↓	low
Savastano et al. (2005)	BMI (unit = kg/m^2), Fat mass (unit = kg, measure = BIA), Weight (unit = kg)	DHEAS (unit = µmol/l, measure = RIA), Cortisol/DHEAS molar ratio (unit = / , measure = calculated from cortisol and DHEAS values)	-	Fat mass, Weight, BMI, Cortisol/DHEAS molar ratio: ↓ ; DHEAS: ↑	low

Kopp et al. (2006)	BMI (unit = kg/m^2), Weight (unit = kg)	Freed_Androgen_inde (unit = /, measure = calculated as total tesosterone/SHBG ratio), SHBG (unit = nmol/l, measure = ELISA system), Androstendione (unit = ng/ml, measure = RIA or ELISA), Testosterone (unit = nmol/l, measure = electrochemiluminescence Immunoassay), DHEAS (unit = µmol/l, measure = ELISA)	-	Weight, BMI, Free_Androgen_index, Androstendione, Testosterone, DHEAS: ↓, SHBG: ↑, significant negative corr. between change BMI and SHBG ↓	low	
Riedt et al. (2006)	BMI (unit = kg/m^2)	Estradiol (unit = pg/ml, measure = RIA), Estrone (unit = pg/ml, measure = RIA)	-	BMI: ↓	low	

Ernst et al. (2013)	BMI (unit = kg/m^2), Waist circum. (unit = cm), Hip circum. (unit = cm)	SHBG (unit = nmol/l, measure = chemiluminescence immunoassay), Testosterone (unit = nmol/l, measure = chemiluminescence immunoassay), Testosterone_bio (unit = nmol/l, measure = calculated by using the method of Vermeulen et. al method), Testosterone_free (unit = nmol/l, measure = chemiluminescence immunoassay), DHEAS (unit = µmol/l, measure = chemiluminescence immunoassay), Freed_Androgen_index (unit = /, measure = calculated as the total testosterone/SHBG ratio Ã— 100)	-	For pre- and post-menopausal women= BMI, waist circumference, hip circumference, Testosterone, Testosterone_free, Testosterone_bio, Freed_Androgen_Index: ↓SHBG: ↑ ; only for pre-menopausal: DHEAS ↓	low
Sarwer et al. (2014)	Weight (unit = kg)	Estradiol (unit = pg/ml, measure = ELISA), Testosterone (unit = ng/dl, measure = ELISA), SHBG (unit = micro gram, measure = ELISA), DHEAS (unit = micro gram, measure = ELISA)	Narrative summary: Same study as Sarwer, 2018	Weight, Estradiol, Testosterone, DHEAS: ↓ ; SHBG ↑	moderate

Sarwer et al. (2018)	Weight (unit=kg)	Estradiol (unit = pg/ml, measure = not stated), Testosterone (unit = ng/dl, measure = not stated), SHBG (unit = nmol/l, measure = not stated), DHEAS (unit = µg/dl, measure = not stated)	Narrative summary for Estradiol: no information about menopausal status	Weight, DHEAS, Testosterone: ↓ SHBG: ↑	moderate
Paul et al. (2020)	Weight(unit = kg), BMI (unit = kg/m^2)	Testosterone (unit = nmol/l, measure=electrochemiluminescence immunoassay with competitive principle), SHBG (unit = nmol/l, measure=electrochemiluminescence immunoassay with sandwich principle)	Blood assay was not drawn in reference to a specific day of the cycle	Weight, BMI: not reported if significant but seems like it ↓, Testosterone: ↓, SHBG: ↑	serious
Beiglböck et al. (2020)	BMI (unit=kg/m^2)	Testosterone (unit = ng/ml, measure=not reported), SHBG (unit = nmol/l, measure=not reported), Testosterone_bio (unit = ng/ml, measure=not reported), DHEAS (unit = µg/ml, measure=not reported), Androstendione (unit = ng/ml, measure=not reported), Estradiol (unit = pg/ml, measure=not reported)	Narrative summary for Estradiol: no information about menopausal status	BMI, Testosterone, Testosterone_bio, DHEAS: ↓ SHBG, Estradiol: ↑	serious

Bastounis et al. (1998)	Weight(unit = kg), BMI (unit = kg/m^2)	Estradiol (unit = pg/ml, measure = RIA), Progesterone (unit = ng/ml, measure = RIA), Testosterone (unit = ng/ml, measure = RIA), Testosterone_free (unit = pg/ml, measure = RIA), Androstendione (unit = ng/ml, measure = RIA), DHEAS (unit = µg/dl, measure = RIA), SHBG (unit = nmol/l, measure = IRMA Count, Diagnostic Products Corp)	-	Weight, BMI: not reported if significant but seems like it ↓; Estradiol, testosterone, Testosterone_free, Androstendione: ↓; SHBG: ↑	moderate
Linkov et al. (2017)	Weight (unit = kg), BMI (unit = kg/m^2), Waist_Circum(unit = cm), WHR	SHBG (unit = not reported, measure = not reported)	Narrative summary: no specific value for SHBG	Weight, BMI, Waist_Circum, WHR: ↓ ; SHBG: ↑	-

Goodfriend et al. (1999)	Mean weight loss was 12.2±1.0 kg (no baseline data), average BMI following weight loss was 29.5 kg/m2 (not mentioned if for women, men or both), VAT decreased (no value mentioned)	Aldosterone (unit = ng/dl, measure = radioimmunoassay), DHEAS (unit = ng/dl, measure = radioimmunoassay)	Narrative summary: Exposure value not clear if for men/-women and not all values (baseline, follow-up); Outcome values just for women	BMI, VAT: ↓ (not mentioned if for women, men or both), Aldosterone: ↓; significant positive correlation between Aldosterone and Fat mass, Aldosterone and BMI and Aldosterone and VAT	moderate
Van Rossum et al. (2000)	Fat mass (unit = kg, measure = /), % Body fat (unit = %, measure = DEXA), BMI(unit = kg/m^2), IAF (unit = cm^2, measure = CT-scan), SAT (unit = cm^2, measure = CT-scan)	SHBG(unit = nmol/l, measure = Immunoradiometric assay)	-	Fatmass, % Bodyfat, BMI, IAF, SAT: ↓	moderate
Ricci et al. (2001)	Fat mass (unit = kg, measure = DEXA)	SHBG (unit = nmol/l, measure = 2-site immunoradiometric assay), Estrone (unit = pmol/l, measure = RIA)	-	Fatmass: ↓, SHBG: ↑	minimal

Kaaks et al. (2003)	Waist_Circum(unit = cm), WHR, Hip Circum(unit = cm), BMI(unit = kg/m^2)	Testosterone_free(unit = ng/ml, measure = calculated from SHBG and total testosterone), Testosterone(unit = ng/ml, measure = RIA), Estradiol(unit = pg/ml, measure = RIA), SHBG(unit = nmol/l, measure = Immunoradiometric kit), Estradiol_free(unit = pg/ml, measure = calculated from SHBG and total estradiol)	Narrative summary: mean was reported but no measure of variance (e.g. SD)	Waist_Circum, WHR, Hip circum., BMI, Testosterone, Testosterone_free, Estradiol_free: ↓, SHBG: ↑	minimal
Bhargava (2006)	BMI (unit = kg/m^2), Waist circum. (unit = m), Hip circum. (unit = m)	SHBG (unit = nmol/l, measure = Immunoradiometric assays), Estradiol (unit = pmol/l, measure = RIA)	-	BMI, Waist circum., Hip circum.: ↓, SHBG: ↑	minimal
Kovacikova et al. (2008)	BMI (unit = kg/m^2), Fat mass (unit = kg, measure = multifrequency bioimpedance), WHR (unit = /), Waist circum. (unit = cm)	Testosterone(unit = nmol L^-1, measure = calculated), Testosterone_free(unit = nmol L^-1, measure = RIA), SHBG(unit = nmol L^-1, measure = RIA)	-	BMI, Fatmass, Waist cirum., WHR, Testosterone_free: ↓, SHBG: ↑	moderate

Harvie et al. (2011)	% Bodyfat (measure = impedance), Weight (unit = kg), Fatmass (unit = kg, measure = impedance)	SHBG(unit = nmol/l, measure = non-competitive IRMA (IRMA-Orion Diagnostica Oy, Espoo, Finland, CV 2.7Percent)), Androstendione(unit = µmol l^-1, meaure = liquid chromatography and tandem mass spectrometry), DHEAS(unit = µmol l ^-1, measure = liquid chromatography and tandem mass spectrometry), Testosterone (unit = nmol l ^-1, measure = liquid chromatography and tandem mass spectrometry), Free_Androgen_Index(unit =&, measure = by the equation 100 serum testosterone/serum SHBG)	-	Weight, % Bodyfat, Fatmass, Free Androgen Index: ↓, SHBG: ↑, only for CER= DHEAS: ↓	minimal

Campbell et al. (2012)	Weight (unit = kg), %bodyfat (unit = %, measure = dual x-ray absorptiometry scanner)	Estrone (unit = pg/ml, measure = RIA), Estradiol(unit = pg/dl, measure = RIA), Testosterone(unit = ng/dl, measure = RIA), SHBG(unit = nmol/l, measure = chemiluminescent immunometric assay using the Immulite Analyzer), Estradiol_free(unit = pg/ml, measure = Calculated using the measured values for estradiol, SHBG, and an assumed constant for albumin), Androstendione(unit = ng/dl, measure = RIA), Testosterone_free(unit = pg/ml, measure = Calculated using the measured values for total testosterone, SHBG, and an assumed constant for albumin.)	-	Weight, % Bodyfat: ↓ (intervention vs. Control group); for Diet group: Estrone, Estradiol, Estradiol_free, testosteroen_free: ↓(intervention vs. Control group), SHBG: ↑(intervention vs. Control group); for Exercise group: Estrone: ↓(intervention vs. Control group); for Diet+Exercise: Estrone, Testosterone, Estradiol, estradiol_free,Testosterone_free: ↓(intervention vs. Control group), SHBG: ↑(intervention vs. Control group)	minimal

Monninkhof et al. (2009)	%Bodyfat (unit = %, measure = DEXA)	Testosterone (unit = pg/ml, measure = double-antibody radioimmunoassay), Testosterone_free (unit = pg/ml, measure = double-antibody radioimmunoassay), Androstenedione (unit = pg/ml, measure = double-antibody radioimmunoassay), Estradiol_free (unit = pg/ml, measure = double-antibody radioimmunoassay), Estradiol (unit = pg/ml, measure = double-antibody radioimmunoassay), Estrone (unit = pg/ml, measure = double-antibody radioimmunoassay), SHBG (unit = nmol/l, measure = double-antibody radioimmunoassay)	Narrative summary: mean was reported but no measure of variance (e.g. SD)	%Bodyfat: ↓ (intervention vs. Control group); Androstenedione, Testosterone, Testosterone_free: ↓ -> values for those that loss > 2% body fat	medium

van Gemert et al. (2015)	Waist circum. (unit = cm), Hip circum. (unit = cm), % Body fat (measure = DEXA), BMI (unit = kg/m^2), Weight(unit = kg), Fat mass (unit = kg, measure = DEXA)	Estradiol (unit = pg/ml, measure = LC-MS), Estrone (unit = pg/ml, measure = LC-MS), Estradiol_free (unit = pg/ml, measure = calculated by using the total hormone levels, SHBG and a constant for albumin), Testosterone (unit = pg/ml, measure = LC-MS), Androstenedione (unit = pg/ml, measure = LC-MS), Testosterone_free (unit = pg/ml, measure = calculated by using the total hormone levels, SHBG and a constant for albumin), SHBG (unit = nmol/l, measure = double-antibody radioimmunoassay)	-	Waist circum., Hip circum., % Bodyfat., BMI, Weight, Fat mass: ↓ (comparison of both intervention groups vs control); for Exercise: Estradiol, Estradiol_free, Testosterone_free: ↓ (for the comparison of both intervention groups vs control), SHBG: ↑ (for the comparison of both intervention groups vs control); for Diet: Estradiol, Estradiol_free: ↓ (for the comparison of both intervention groups vs control), SHBG: ↑ (for the comparison of both intervention groups vs control)	minimal
Rock et al. (2016)	Weight (unit = kg)	SHBG (unit = nmol/l, measure = chemiluminescent sandwich techniques)	stratified results for estradiol but not SHBG	Weight: ↓ ; for lowfat and walnut rich group= SHBG:↑	maximal

Swora-Cwynar et al. (2016)	BMI (unit = kg/m^2), Fat mass (unit = kg, measure = BIA), Weight (unit = kg), % Bodyfat (measure = BIA)	Testosterone (unit = nmol/l, measure = electrochemiluminescent immunoassay), DHEAS (unit = µg/dl, measure = electrochemiluminescent immunoassay), Estradiol (unit = pg/ml, measure = electrochemiluminescent immunoassay)	-	BMI, Fatmass, Weight, %Bodyfat: ↓, significant positive correlation between change fatmass and change Testosterone & change BMI and change Testosterone	maximal
O'dea et al. (1979)	Weight (unit = kg)	Estradiol (unit =p g/ml, measure = RIA), Testosterone (unit = ng/dl, measure = measured as unfractionated 17beta-ol androgens), SHBG (unit = no unit mentioned, measure = DHT saturation)	-	Weight, Estradiol: ↓, SHBG:↑	moderate

Leenen et al. (1994)	WHR, VAT(unit = cm^2, measure = MRI), Weight (unit = kg), Abdominal fat area (SC) (unit = cm2, measure = magnetic resonance imaging), Fat mass (unit = kg), BMI (unit = kg/m^2)	Estrone (unit = pmol/l, measure = LH-20 columns using toluene-methanol (92:8, vol/vol) as eluent and quantitated by RIA), Estradiol (unit = pmol/l, measure = RIA), Estradiol_free (unit = pmol/l, measure = calculated from shbg and total estradiol), Testosterone (unit = nmol/l, measure = RIA), SHBG (unit = nmol/l, measure = Immunoradiometric assay), Testosterone_free (unit = nmol/l, measure = Calculated from total T and SHBG), freeE2/FreeT_ratio (unit = /, measure = calculated from Free E2 and Free T), DHEAS (unit = µmol/l, measure = RIA)	-	WHR, VAT, Weight, Abdominal fat area, Fat mass, BMI, Estradiol, Estradiol_free, Testosterone, Testosterone_free: ↓, SHBG, DHEAS:↑; WHR and SHBG, WHR and Estradiol, WHR and Estradiol_free, WHR and freeE2/FreeT_ratio, VAT and SHBG, VAT and freeE2/FreeT_ratio, VAT change and SHBG, VAT change and freeE2/FreeT_ratio : significant negative correlation; VAT and Testosterone_free: significant positive association	low
Kraemer et al. (2003)	% Bodyfat (unit = %, measure = determined using body-density and Siri equation)	SHBG (unit = nmol/l, measure = double antibody liquid phase RIA)	-	%Bodyfat: ↓	minimal

Caballero and Maynar (1992)	Skinfolthickness_suprailiac (measure = Harperiden skinfold caliper), Skinfolthickness_subscapular (measure = Harperiden skinfold caliper), %Bodyfat (unit: %), Skinfolthickness_triceps (measure = Harperiden skinfold caliper)	SHBG (unit = nmol/l, measure = endogeneous steroids were removed from plasma with charcoal suspension, then incubation and free steroid was removed using charcoal suspension, SHBG was expressed in terms of a molar concentration of bound 3H-DHT after substraction of non-specific bindin)	-	Skinfolthickness_suprailiac, Skinfolthickness_subscapular, %Bodyfat, Skinfolthickness_triceps, SHBG: ↓	low
McTiernan et al. (2004a)	%Bodyfat (extracted for group that lost >2%)	Testosterone_free (unit = pg/ml, measure = calculated using the measured testosterone and sex hormone binding globulin (immunometric assay) concentrations and an assumed constant for albumin), Androstenedione (unit = pg/ml, measure = RIA), Testosterone (unit = pg/ml, measure = RIA), DHEA (unit = ng/ml, measure = RIA), DHEAS (unit= g/dL, measure = competitive immunometric assay)	Narrative summary: data for participants that lost > 2% body fat	Testosterone_free, Testosterone: ↓	minimal

Campbell et al. (2007)	Fat mass (unit = kg, measure=dual-energy X-ray absorptiometry), %Bodyfat (unit = %, measure = dual-energy X-ray absorptiometry)	16-alpha_OHE-1 (unit = ng/mg CR, measure = ELSIA), 2-OHE-1 (unit = ng/mg Cr, measure = ELSIA), Ratio_2OHE1_to_16OHE1 (unit = ratio, measure = no unit)	Narrative summary: only studies that measured these specific sex steroids	Fatmass , %Bodyfat: ↓ (intervention vs. Control group)	minimal
Friedenreich et al. (2010)	Weight change (unit = kg)	Estradiol (unit = pg/ml, measure = RIA), SHBG (unit = nmol/l, measure = immunometric assay using the Immulite Analyzer), Estrone (unit = pg/ml, measure = RIA), Androstenedione (unit = pg/ml, measure = RIA), Testosterone (unit = ng/dl, measure = RIA), Estradiol_free (unit = pg/ml, measure = calculated from SHBG, E2 and assumed albumin concentration of 43 g/L), Testosterone_free (unit = ng/dl, measure = calculated from SHBG, T and assumed albumin concentration of 43 g/L)	Narrative summary: only change of weight is reported	Weight change, Estradiol, Estradiol_free: ↓ (intervention vs. Control group), SHBG:↑ (intervention vs. Control group)	minimal

Kim and Kim (2012)	Waist_Circum (unit = cm, measure = by clinician, % Bodyfat (unit = %, measure = BIA), BMI (unit = kg/m^2, measure = by clinician), VAT (unit = cm^2, measure = BIA)	SHBG (unit = µg/ml, measure = IRMA)	-	Waist_Circum, % Body fat, BMI, VAT: ↓, SHBG:↑	minimal
Boyden et al. (1983)	Fat mass (unit = kg), relative fat %	Estrone (unit = pg/ml, measure = radioimmunoassay), Estradiol (unit = pg/ml, measure = radioimmunoassay), Testosterone (unit = pg/ml, measure = radioimmunoassay), Testosterone_free (unit = %, measure = estimated by centrifugal ultrafiltration dialysis with the use of the MPS-1 micropartition system)	-	Fat mass, relative fat %, Estradiol: ↓	low

McTiernan et al. (2004b)	%Bodyfat (extracted for group that lost >2%)	Estrone (unit = pg/ml, measure = radioimmunoassay), Estradiol (unit = pg/ml, measure = radioimmunoassay), SHBG (unit = nmol/l, measure = immunometric assay using the Immulite Analyzer (Diagnostic Products Corporation, Los Angeles, CA)), Estradiol_free (unit = pg/ml, measure = calculated using the measured values for estradiol and SHBG and an assumed constant for albumin)	Narrative summary: data for participants that lost > 2% body fat	Estradiol, Estradiol_free: ↓ (for hormone change from baseline between exercisers and controls for that level of fat change versus gained body fat)	minimal
Sowers et al. (2001)	Fat mass (unit = kg, measure = DEXA), % Body fat (unit = %, measure = DEXA), BMI (unit = kg/m^2, measure = clinician)	Testosterone (unit = pg/ml, measure = RIA)	Narrative summary: no intervention	Fatmass, %Bodyfat, BMI: ↑	minimal

	Goss et al. (2012)	IAAT (unit = cm^2, measure = CT)	Estradiol (unit = pg/ml, measure = RIA or IRMA), Estrone (unit = pg/ml, measure = RIA or IRMA), Testosterone_free (unit = pmol/L, measure = RIA or IRMA), Androstenedione (unit = ng/ml, measure = RIA or IRMA), DHEAS (unit = µg/dl, measure = RIA or IRMA), Testosterone (unit = ng/dl, measure = RIA or IRMA), SHBG (unit = ng/ml, measure = RIA or IRMA)	Narrative summary: no intervention	IAAT, SHBG: ↑ (but p value for HRT useres/non-users combined, not only HRT non-users), Androstenedione: ↓ (but p value for HRT useres/non-users combined, not only HRT non-users), significant negative association for Testosterone_free and IAAT, significant positive association for SHBG and IAAT	medium	

Aubuchon et al. (2016)	Weight (unit = kg), VAT (unit = cm^2, measure=computed tomography), %Bodyfat (measure = dual x-ray absorptiometry), BMI (unit = kg/m^2)	logTestosterone (unit = ng/dl, measure = Immulite 1000 solid phase chemiluminescent immunoassay (Siemens Medical Solutions Diagnostics, Flanders, NJ, USA)), logSHBG (unit = nmol/l, measure = Immulite 1000 solid phase chemiluminescent immunoassay (Siemens Medical Solutions Diagnostics, Flanders, NJ, USA)), logFreed_Androgen_index (measure = calculated from Testosterone and SHBG), Testosterone (unit = ng/dl, measure = Immulite 1000 solid phase chemiluminescent immunoassay (Siemens Medical Solutions Diagnostics, Flanders, NJ, USA)), SHBG (unit = nmol/l, measure = Immulite 1000 solid phase chemiluminescent immunoassay (Siemens Medical Solutions Diagnostics, Flanders, NJ, USA))	-	Weight, VAT, Body_fat_percentage, BMI, logFree_Androgen_index: ↓, logSHBG: ↑	medium

Van Gemert et al. (2017)	SAAT (unit = cm^2, measure = magnetic resonance imaging), IAAT (unit = cm^2, measure = magnetic resonance imaging), Fat mass (unit = kg, measure = DEXA)	Estradiol_free (unit = pg/ml, measure = LC-MS), Testosterone_free (unit = pg/ml, measure = LC-MS), SHBG (unit = nmol/l, measure = RIA)	-	SAAT, IAAT, Fat mass, Estradiol_free, Testosterone_free: ↓ not reported if significant or not but seems like it is (change >10% for body composition measurements), SHBG: ↑ not reported if significant or not but seems like it is	minimal	

	Duggan et al. (2019)	Weight change (unit = %) -> data was only extracted for group with weight loss >10%	Estradiol_free (unit = pg/ml, measure = calculated using measured values for total estradiol, SHBG, and an assumed constant for albumin), SHBG(unit = nmol/l, measure = quantified via chemiluminescent immunometric assay using the Immulite Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL)), Estradiol(unit = pg/ml, measure = radioimmunoassay after organic solvent extraction and Celite column partition chromatography), Testosterone(unit = ng/dl, measure = radioimmunoassay after organic solvent extraction and Celite column partition chromatography), Estrone(unit = pg/ml, measure = radioimmunoassay after organic solvent extraction and Celite column partition chromatography), Testosterone_free(unit = pg/ml, measure = calculated using measured values for total testosterone, SHBG, and an assumed constant for albumin.)	Narrative summary: data for category of weight loss >10%	Weight change: not reported if significant but seems like it ↓, Testosterone_free, Estradiol_free: ↓, SHBG: ↑	medium

FRIEDMAN et al. (1982)	Weight (unit = kg)	Testosterone_free(unit = pg/ml, measure = RIA), SHBG (unit = nM, measure = charcoal absorption assay), Testosterone (unit = ng/dl, measure = RIA)	-	Weight, Testosterone_free: ↓, SHBG: ↑	moderate
Svendsen et al. (1995)	Weight (unit = kg), VAT(unit = cm^2, measure = predicted with an equation), Fat mass (unit = kg, measure = DEXA)	SHBG (unit = nmol/l, measure = IRMA), Testosterone (unit = nmol/l, measure = RIA), Androstenedione (unit = nmol/l, measure = RIA), Estradiol (unit = pmol/l, measure = RIA)	-	Weight, VAT, Fat mass: not reported if significant but seems like it ↓, Gynoid and Android group (not reported but seems like it) = SHBG: ↑, change SHBG and Fat mass: significant negative correlation, change SHBG and WTH: significant negative correlation	maximal

Stolzenberg-Solomon et al. (2012)	Weight (unit = kg)	Androstenedione (unit = pg/ml, measure = RIA), Estrone (unit = pg/ml, measure = RIA), Estradiol (unit = pg/ml, measure = RIA), Testosterone (unit = ng/dl, measure = RIA), DHEAS (unit = g/dl, measure = RIA), SHBG (unit = nmol/l, measure = RIA), Estradiol_free (unit = pg/ml, measure = calculated from measured estradiol and SHBG with albumin assumed to be a constant (40 g/l) using the method by Sodergard and colleagues according to the law of mass action), Testosterone_free (unit = pg/ml, measure = calculated from measured Testosterone and SHBG with albumin assumed to be a constant (40 g/l) using the method by Sodergard and colleagues according to the law of mass action)	-	Weight, Estrone, Estradiol, Estradiol_free, Testosterone_free: ↓, SHBG: ↑	medium

Table A.2.: Study analysis summary table. Risk of Bias (ROB), Body mass index (BMI), visceral adipose tissue (VAT), intra-abdominal fat (IAF), intra-abdominal adipose tissue (IAAT), subcutaneous adipose tissue (SAT), subcutaneous abdominal adipose tissue (SAAT), (BIA), Radioimmunoassay (RIA), Immunoradiometric assay (IRMA), Dual Energy X-ray Absorptiometry (DEXA), Enzyme-linked Immunosorbent Assay (ELISA), Computed tomography (CT), Liquid chromatography–mass spectrometry (LC-MS), Dihydrotestosterone (DHT), Dehydroepiandrosterone-sulfate (DHEAS), Sex hormone binding globulin (SHBG), (E2), continuous energy restriction (CER), hormone replacement therapy (HRT)