Thieme

Lifestyle Interventions to Improve Pregnancy Outcomes: a Systematic Review and Specified Meta-Analyses

Lebensstil-Interventionen zur Verbesserung von Schwangerschaftsergebnissen: eine systematische Auswertung und vorab spezifizierte Metaanalysen

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ABSTRACT

To compare the impact of lifestyle interventions for overweight and obese pregnant women a systematic review and meta-analysis was conducted using pre-registration and audit of the interventions as selection criteria.

PubMed, Web of Science and CENTRAL were searched for randomized controlled trials examining diet, exercise, combined interventions or associated behavioral therapy. Trials were selected if they reported one of the primary outcomes (gestational diabetes, hypertensive disorders, perinatal mortality, admission to neonatal intensive care unit). Results were established from the total group and separately from pre-registered or clinically audited studies.

Out of 1304 titles, 28 randomized controlled trials were included. Among the primary outcomes only hypertensive disorders were significantly reduced by exercise in the total group: odds ratio 0.52 (95 % confidence interval 0.28 to 0.96, four trials, 1324 participants). When behavioral therapy supported combined interventions, maternal weight gain, (Standardized Mean Difference − 0.16 kilogram; 95 % confidence interval − 0.28 to − 0.04, four trials, 2132 participants) and neonatal birthweight, (Standardized Mean Difference − 0.4 gram; 95 % confidence interval − 0.62 to − 0.18, five trials, 1058 participants), were significantly reduced within the total group and both specified meta-analyses. Higher frequencies of physical activity improved the results. Risk of bias, assessed with the Cochrane Tool, was low to moderate.

Elements of behavioral therapy might better prevent adverse effects of maternal obesity when combined with lifestyle interventions. Unfortunately, high heterogeneity due to different intervention and population characteristics was a limiting factor. Future studies should also focus on increased intensities of physical activity.

ZUSAMMENFASSUNG

Das Ziel war, die Auswirkungen von Lebensstil-Interventionen auf übergewichtige und adipöse Schwangere zu vergleichen. Dazu wurde eine systematische Auswertung der Literatur mit spezifizierten Metaanalysen durchgeführt; Auswahlkriterien

waren Registrierung vor Studiendurchführung und Prüfung von Interventionen.
Die Datenbanken PubMed, Web of Science und CENTRAL wurden nach randomisierten kontrollierten Studien durchsucht, welche die Auswirkungen von Ernährung, körperlicher Betätigung, kombinierten Interventionen sowie damit assoziierten Verhaltenstherapien untersuchten. Studien wurden in die Auswertung aufgenommen, wenn sie Informationen über Primärergebnisse (Gestationsdiabetes, Hypertonie, perinatale Sterblichkeit, Aufnahme auf eine Intensivstation für Früh- und Neugeborene) enthielten. Die Ergebnisse wurden für die Gesamtgruppe sowie separat für im Vorfeld registrierte oder klinisch geprüfte Studien ermittelt.
Aus insgesamt 1304 Publikationen wurden 28 randomisierte kontrollierte Studien ausgewählt und in die Auswertung aufgenommen. Bei den Primärergebnissen zeigte sich, dass in der Gesamtgruppe nur die Hypertonie durch mehr körperliche Betätigung signifikant reduziert werden konnte: Odds Ratio (OR) 0,52 (95 %-Konfidenzintervall [KI] 0,28–0,96, 4 Studien, 1324 Teilnehmer). Wenn kombinierte Interventionen durch eine Verhaltenstherapie unterstützt wurden, kam es innerhalb der Gesamtgruppe sowie in den spezifizierten Metaanalysen zu einer deutlichen Reduzierung der mütterlichen Gewichtszunahme, (standardisierter Mittelwertdifferenz − 0,16 Kg; 95 %-KI − 0,28 bis − 0,04, 4 Studien, 2132 Teilnehmer) und des neonatalen Geburtsgewichts (standardisierter Mittelwertdifferenz − 0,4 g; 95 %-KI − 0,62 bis − 0,18, 5 Studien, 1058 Teilnehmer). Höhere Häufigkeiten bei der körperlichen Betätigung verbesserten die Ergebnisse. Das mit dem Cochrane-Tool bewertete Verzerrungspotenzial war gering bis mäßig.
Elemente der Verhaltenstherapie können die negativen Auswirkungen einer mütterlichen Adipositas besser verhindern, wenn sie mit Lebensstil-Interventionen kombiniert werden. Leider war die hohe Heterogenität infolge der unterschiedlichen Interventionen und Bevölkerungscharakteristiken ein limitierender Faktor. Künftige Studien sollten ihr Augenmerk auch auf die Intensität der körperlichen Betätigung richten.

Introduction

The global rise in rates of overweight and obesity among women of reproductive age leads to an increase in adverse pregnancy outcomes [1]. Main drivers are the transition from an active to a sedentary lifestyle, the frequent consumption of high-calorie food and high social deprivation [2]. However, maternal obesity does not only affect short-term pregnancy outcomes, the impaired long-term effects on mothers and their offspring cause the rising numbers of non-communicable diseases [3, 4, 5]. The epigenetic transgenerational passage of non-communicable diseases related to overweight and obesity to second and third generations is a vicious circle with an urgent need for innovative solutions.

In experiments with obese pregnant rats, dietary and physical activity interventions translated into relevant changes in phenotype, stress responses and metabolic characteristics in the offspring suggesting similar effects in humans [6]. Four narrative reviews have addressed human maternal obesity and the urgent need for effective interventions tailored to ethnicity and culture whereby "top-down" imposed political strategies were contrasted to patient motivated "bottom-up" approaches [3, 7, 8, 9].

Pregnancy provides a point of contact with healthcare providers and thus can be utilized to promote lifestyle changes. In addition, women might become motivated to change their lifestyle in the interest of their baby [10]. Nevertheless, there is a lack of uniform protocols describing how to respond to maternal obesity during pregnancy [11, 12]. Besides, randomized controlled trials (RCT) rarely apply uniform statistical methods nor uniform clinical care with respect to the kind and frequency of interventions and psychological support of participants.

It was our aim to perform a systematic review and different meta-analyses investigating lifestyle interventions specifically designed to limit adverse effects of obesity during pregnancy. Thereby, we underlied the hypothesis that the negative effects of maternal overweight and obesity (BMI > 25 kg/m^2) on maternal and fetal outcomes could be limited by different non-pharmacological interventions and even be improved by well audited frequent interventions or the combined use of behavioral therapy [13].

Furthermore, we assessed if there was an audit to check if participants followed the intervention guidelines (e.g. questionnaires, pedometers, fitness tests, food records) and if the studies were pre-registered (pro-actively registered in an international registry of clinical trials). Thus, the total group of RCTs and subgroups consisting of only pre-registered RCTs, or only RCTs with clinically audited interventions were compared [14].

Material and Methods

Data sources

We conducted a systematic review by searching for RCTs within PubMed, Web of Science and Cochrane Central Register for Clinical trials (CENTRAL) up to January 2021, without date or language restrictions. The primary outcomes "gestational diabetes", "gestational hypertension", "pre-eclampsia", "perinatal mortality" and "NICU admission" were used as search terms coupled with the following: "maternal", "pregnancy", "obstetrics", "gestation", "delivery", "perinatal", "random", "weight gain", "overweight", "obesity". We adapted the systematic search to the requirements of each database. Reference lists of obtained articles were additionally hand-searched. Abstracts and unpublished studies were not considered. Two authors independently screened titles, abstracts, and full texts of potentially eligible studies via COVIDENCE [15]. Any disagreement was resolved through discussion with a third reviewer.

Main outcome measures

Hypertensive disorders in pregnancy (HDP) and GDM, the most frequent maternal diseases associated with overweight and obe-

sity, as well as perinatal mortality and admission to the neonatal intensive care unit (NICU), the most severe fetal outcomes, were defined as primary outcomes [1]. Thereby, HDP included the diagnosis of gestational hypertension and preeclampsia according to the definition of the American College of Obstetricians and Gynaecologists [16]. We defined gestational diabetes following the criteria of the International Association of the Diabetes and Pregnancy study Groups: Diabetes that was first diagnosed in the second or third trimester of pregnancy and not clearly overt prior to gestation [17]. The definition of perinatal mortality included the number of fetal deaths past 20 completed weeks of pregnancy added to the number of deaths among live-born children up to seven completed days of life. NICU admission consisted of the number of children transferred to a neonatal intensive care unit for at least one day, as well as infants admitted to a special care baby unit if reported.

Secondary outcomes

As overweight and obese pregnant women are at increased risk for excessive gestational weight gain, we selected maternal gestational weight gain (GWG), and the rates of women with a GWG exceeding the recommendations of the Institute of Medicine (IOM) as secondary outcomes [18, 19]. Obesity and excessive gestational weight gain similarly increase risks of caesarean delivery, preterm birth < 37 gestational weeks, and the rates of large- or small-for-gestational-age (LGA or SGA) infants, defined by a birthweight ≥ 90^{th}, respectively < 10^{th} centile of the referred population. Thus, we defined these outcomes as secondary outcomes in addition to neonatal birthweight in total [20, 21].

Eligibility criteria

RCTs were included which provided data of at least one of our primary outcomes in singleton pregnancies, targeted a population of women who were classified as overweight or obese according to WHO definition (pre-pregnancy body mass index [BMI] ≥ 25 kg/m^2, respectively ≥ 30 kg/m^2) and compared the effect of non-pharmacological interventions with the intention to realize lifestyle changes during pregnancy with controls receiving routine treatment or general advice [13, 22]. Criterion for being included in this systematic review and meta-analysis was the content of interventions; either diet or exercise or a combination of both. Eligible interventions ranged from simple counselling or written information about the need for eating healthy and exercising during pregnancy up to scheduled regular classes and workshops for practicing a healthy lifestyle. Interventions were then separately analyzed according to their content. Additionally, we investigated if combined interventions were accompanied by behavioral therapy.

Studies targeting women with maternal co-morbidities diagnosed prior to the start of the trial such as diabetes mellitus Type 1 or 2, gestational diabetes mellitus (GDM) or polycystic ovarian syndrome were excluded.

Two authors independently assessed the risk of bias with the Cochrane tool via COVIDENCE [15, 23]. Thereby, random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and (if applicable) blinding of participants, personnel and outcome assessment were evaluated.

In general, an audit examines if processes or activities meet required standards or guidelines. In this meta-analysis, we assessed if there was any sort of audit to check if participants followed the intervention guidelines. Trials realized an audit e.g., by questionnaires, counting the number of participants in exercise sessions, pedometers, fitness tests, food records or consistent weight control. Studies were defined as pre-registered when they were proactively registered in an international registry of clinical trials.

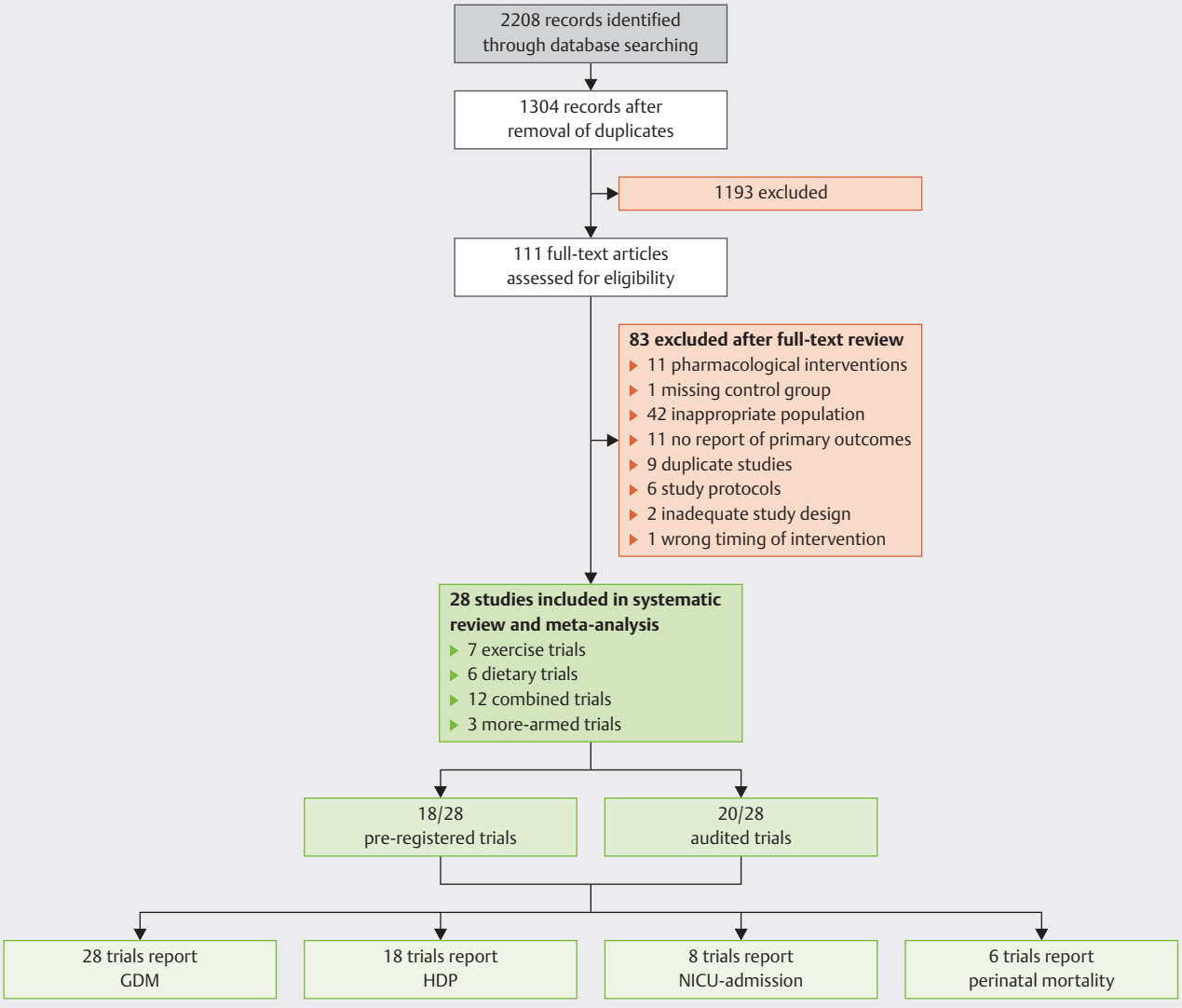
Data collection and analysis

Summary estimates were collected within a standardized excel sheet. In case of missing information, the corresponding authors were contacted via e-mail.

For all included RCTs, we extracted pre-defined primary and secondary outcomes, characteristics of study registration, inclusion and exclusion criteria, and patient characteristics. Dropout rates, intervention and control conditions, and the risk of bias were analyzed. We followed the Cochrane handbook to identify duplicate publications [24]. Template data collection forms, analytic code and data used for all analyses are not publicly available but can be requested from the authors.

For statistical analysis, we used R (version 3.4.3) and the package R meta [25]. Odds ratios, respectively standardized mean differences were calculated using the given numbers of events, respectively the given means, standard deviations and numbers of participants in each group. Separate random-effects meta-analyses were performed for the total group and for only pre-registered and only audited RCTs. The study arms of trials that had included more than one intervention were analyzed separately. Results were presented using Forest plots. We expressed effects for dichotomous outcomes by odds ratios (ORs) and for continuous outcomes by standardized mean differences (SMD); for both, 95 % confidence intervals (CI) were calculated. SMD values of 0.2–0.5 were interpreted as a small effect, values of 0.5–0.8 as medium, and values > 0.8 as a large effect [26]. The results were pooled using the Mantel Haenszel method, as suggested for facing rare events in studies with zero cell counts [24]. Heterogeneity was assessed by determining the χ^2 test and the I^2 statistics, considering an $I^2 \geq 50\,\%$ indicative for substantial heterogeneity. In case of high heterogeneity it was planned to use Inverse Variance method in comparison. To identify factors that contribute to heterogeneity when there were at least 10 RCTs as recommended we applied meta-regression [24]. We analyzed the frequency and the start of interventions as potential effect modifiers. For the sensitivity analysis, we experimentally excluded each RCT and in a second step all RCTs with a high risk of bias from calculating the overall result. Funnel plots assessed publication bias if there were more than 10 RCTs per meta-analysis.

We pre-registered our study with PROSPERO and followed the PRISMA criteria for reporting systematic reviews and meta-analyses [27]. Prospero registration number: CRD42018089009. URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018089009. We did not prepare a review protocol in addition to the registration protocol. We decided to perform subgroup analyses according to pre-registration and audit of interventions after



▶ **Fig. 1** Flow chart illustrating the study selection process. GDM = gestational diabetes mellitus; HDP = hypertensive disorders in pregnancy; NICU = neonatal intensive care unit.

publishing the protocol but before performing the systematic search.

Review

General characteristics of the studies

The literature search resulted in 1304 records and 28 RCTs with 11 416 participants were included by consensus (▶ **Fig. 1**).

Trials that met the inclusion criteria and were published between January 2008 and January 2021 (n = 28; ▶ **Table 1**) consisted of seven trials investigating physical activity [28][29, 30, 31, 32, 33, 34], six trials with diet [35, 36, 37, 38, 39, 40], and 12 trials with combined interventions [41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52]. Out of those, four study groups had additionally implied behavioral therapy [49, 50, 51, 52]. Three trials investigated two or more arms vs controls [53, 54, 55]. The authors of the trials defined exercise as simple counselling [54, 55], aerobic training [30], a mix of aerobic and strength training [29, 31, 32, 33], an individualized program [34], or did not provide a further specification [28]. Dietary interventions included counselling [35, 36, 37, 38, 54], a Mediterranean diet [40], and a low-glycemic index diet supported by a mobile phone application [47]. Participants of combined interventions were "only" counselled [41, 42, 43, 46, 47, 54], given a brochure [53], or offered a supervised program [44, 45, 48, 55]. Goal setting [53, 50, 52], group sessions [53, 52], increasing self-efficiency [51], control- and social cognitive theory [49][50], and motivational interviewing [52] were additionally applied to increase the compliance of participants. One RCT investigated two different combined interventions vs controls: (1) a brochure and (2) group sessions promoting a healthy lifestyle during pregnancy [53]. Both arms were combined as methodologically explained by the Cochrane Handbook [24].

▶**Table 1 List of studies included.** Trials were classified by their intervention category and sorted alphabetically. If the trial compared more than one intervention arm, each arm was listed separately.

		Intervention characteristics			Details of registration		
Author, Year	**N (Details)**	**Details**	**Start, Frequency**	**Audit**	**Number**	**Date of registration**	**Start of trial**
Exercise							
Barakat et al., 2016 [31]	222 (Subgroup BMI > 25 kg/m^2)	Aerobic exercise, aerobic dance, muscular strength, flexibility	Week 9–11, 3 d/week until week 38–39	No audit	NCT01723098	2012–12–01	2009–02–01
Callaway et al., 2010 [34]	50 (BMI > 30 kg/m^2)	Individualized exercise program	Week 12, 6 sessions, further support by e-mail and telephone	Questionnaire	ACTRN01260 6000271505	2006–06–01	2006–07–01
Daly et al., 2017 [29]	88 (BMI > 30 kg/m^2)	Weightlifting, aerobic exercise	Week 17, 3 d/week until 6 weeks post partum	No audit	ISRCTN 31 045 925	2013–10–01	2013–11–01
Garnaes et al., 2016 [32]	91 (BMI > 28 kg/m^2)	Treadmill, walking/ jogging, and resistance band training	Week 12–14, 3 d/ week until delivery	Adherence to classes	NCT0124355	2010–09–01	2010–09–01
Nobles et al., 2018 [28]	241 (BMI > 25 kg/m^2 high risk for GDM)	Exercise, not defined	Week 12–16, 1 face to face visit, weekly phone calls, mailed information	No audit	Not registered	NA	NA
Oostdam et al., 2012 [33]	101 (BMI > 30 kg/m^2 high risk for GDM)	Aerobic and strength training	Week 15, 2 d/week until delivery	Adherence to classes	NTR1139	2007–11–01	2007–10–01
Renault et al., 2014 [55] *	259 (BMI > 30 kg/m^2)	Exercise counselling	Week 16, one session, a reminder to measure steps every 4 weeks	Pedometer	NCT01345149	2011–04–01	2009–04–01
Simmons et al., 2017 [54] *	213 (BMI > 29 kg/m^2)	Exercise counselling, handbook, educational material, resistance band training	Week 20, 5 sessions, up to 4 phone calls	Questionnaire	ISRCTN 70 595 832	2011–12–01	2012–09–01
Wang et al., 2017 [30]	300 (BMI > 24 kg/m^2)	Supervised stationary cycling, general advice about exercise	Week 12, 3 d/week until week 36–37	Adherence to classes	NCT02304718	2014–11–01	2014–12–01
Diet							
Al Wattar et al., 2019 [39]	795 (Subgroup BMI > 30 kg/m^2)	Mediterranean diet, individual and group sessions, recipe book	Week 18, one individual session, followed by 2 group sessions	Questionnaire, Adherence to classes	NCT02218931	2014–08–18	2014–09–12
McCarthy et al., 2016 [35]	382 (BMI > 25 kg/m^2)	Dietary advice, Counselling about self-control of weight	Week 20, one session	Self-weighting records	Not registered	NA	NA
Osmundson et al., 2016 [36]	33 (Subgroup BMI > 30 kg/m^2, prediabetic)	Counselling about diet, self-monitoring of blood glucose	Week 14, every 2 weeks	No audit	NCT01552213	2012–03–01	2012–03–01
Quinlivan et al., 2011 [38]	124 (BMI > 25 kg/m^2)	Counselling about self-control of weight	Each routine antenatal visit	No audit	ACTRN1260 5000709640	2005–10–01	2005–03–01
Simmons et al., 2017 [54] †	215 (BMI > 29 kg/m^2)	Dietary counselling, handbook/ educational material	Week 20, 5 sessions, up to 4 phone calls	Questionnaire	ISRCTN 70 595 832	2011–12–01	2012–09–01

▶Table 1 continued

		Intervention characteristics			Details of registration		
Author, Year	**N (Details)**	**Details**	**Start, Frequency**	**Audit**	**Number**	**Date of registration**	**Start of trial**
Thomson et al., 2016 [37]	55 (Subgroup BMI > 25 g/m^2)	Education on healthy eating and weight control	Week 19, monthly group meetings, additional home visits	No audit	NCT01746394	2012–12–12	2013–01–01
Zhang et al., 2019 [40]	400 (BMI > 24 kg/m^2)	Low glycemic index diet, mobile phone app, planning of diet with a dietician	Week 14–16, 3 antenatal visits, monthly phone calls	Attendance for interview sessions	NCT01628835	2012–06–27	2012–06–30
Diet and exercise							
Bogaerts et al., 2013 [53] ‡	121 (BMI > 29 kg/m^2)	Brochure of diet and physical activity, information to limit excessive GWG	Week 15, once	No audit	Not registered	NA	NA
Bruno et al., 2017 [41]	191 (BMI > 25 kg/m^2)	Counselling on hypocaloric (1500 kcal/d), low-glycemic, low-saturated-fat diet and exercise	Weeks 9–12, once, 4 × follow up	Pedometer, Questionnaire	NCT01783210	2013–01–01	2005–07–04
Dodd et al., 2014 [43]	2202 (BMI > 25 kg/m^2)	Counselling on healthy eating and physical activity	Week 10–22, 3 sessions, 3 phone calls	Workbook	ACTRN1260 7000161426	2007–03–01	2008–05–01
Eslami et al., 2018 [47]	140 (BMI > 25 kg/m^2)	Group session with information about healthy lifestyle, text messages, booklet	Week 16–20, single 60–90 min. group session	No audit	IRCT20160 41210324 N31	2016–06–01	2016–05–04
Petrella et al., 2014 [44]	63 (BMI > 25 kg/m^2)	Diet (1500 kcal per day), exercise (30 min 3 × weekly)	Week 12, single session	Pedometer, questionnaire	Not registered	NA	NA
Renault et al., 2014 [55] ‡	264 (BMI > 30 kg/m^2)	Dietary advice (hypocaloric, low fat, 1200–1675 kcal per day), encouragement to increase physical activity	Week 16, every 2 weeks until delivery	Pedometer	NCT01345149	2011–04–01	2009–04–01
Simmons et al., 2017 [54] ‡	218 (BMI > 29 kg/m^2)	Physical activity counselling, handbook, educational material, resistance band training	Week 20, 5 sessions, up to 4 phone calls	Questionnaire	ISRCTN 70595832	2011–12–01	2012–09–01
Thornton et al., 2009 [46]	232 (BMI > 30 kg/m^2)	Counselling, advice about daily exercise	Week 12–18, at each routine antenatal visit	Food records	NCT00740766	2008–08–01	1998–06–01
Van Horn et al., 2018 [48]	280 (BMI > 25 kg/m^2)	Diet, increased activity, increased sleep, supported by a smartphone application	Week 16, 3 individual and 6 group-based sessions	Use of smartphone application	NCT01631747	2012–06–29	2012–11–01
Vinter et al., 2014 [45]	304 (BMI > 30 kg/m^2)	Weekly exercise, free fitness membership during pregnancy, individual dietary counselling	Week 10, 4 dietary counselling sessions, weekly exercise	Fitness test, questionnaire	NCT00530439	2007–09–01	2007–10–01
Zhang et al., 2015 [42]	256 (BMI > 25 kg/m^2)	Education	Week 12	No audit	Not registered	NA	NA

▶Table 1 continued

Author, Year	N (Details)	Intervention characteristics			Details of registration		
		Details	Start, Frequency	Audit	Number	Date of registration	Start of trial
Diet and exercise with behavioral therapy							
Bogaerts et al., 2013 [53] §	139 (BMI > 29 kg/m^2)	Group sessions, goal setting	Week 15, 4 sessions	No audit	Not registered	NA	NA
Harrison et al., 2013 [51]	228 (BMI > 25 kg/m^2, high risk for GDM)	Behavioral change strategies, goal setting, self-efficacy	Week 14–16, 4 sessions	Pedometer, Questionnaire	ACTRN1260 8000233325	2008–05–01	2008–06–01
Kennelly et al., 2018 [49]	565 (BMI 25–39 kg/m^2)	Sessions based on control- and social cognitive theory, smartphone-app	Week 10–17, 3 visits, e-mails every 2 weeks	Questionnaire	ISRCTN 29316280	2013–01–01	2013–01–01
Poston et al., 2015 [50]	1555 (BMI > 25 kg/m^2)	Counselling based on control theory, social cognitive theory, goal setting	Week 15–19, 8 sessions once a week	Questionnaire	ISRCTN 89971375	2008–11–01	2009–11–01
Vesco et al., 2014 [52]	114 (BMI > 30 kg/m^2)	Group sessions, motivational interviewing, goal setting	week 10–20, weekly until delivery	Pedometer, Food records	NCT00950235	2009–07–01	2009–10–01

* Exercise arm, † Diet arm, ‡ Diet and Exercise arm, § behavioral therapy arm. BMI = Body mass index (kg/m^2); d = days; GWG = gestational weight gain; N = Number of participants; NA = not applicable

All RCTs were conducted in high- or middle income countries, 13/28 in Europe [29, 31, 32, 33, 36, 39, 41, 44, 49, 50, 53, 54, 55], 6/28 in the US [28, 37, 45, 46, 48, 52], 5/28 in Australia [34, 35, 38, 43, 51], 3/28 in China [30, 40, 42], and 1/28 in Iran [47]. Baseline characteristics and dropout rates did not differ between intervention and control groups but varied among the singular RCTs.

According to Cochrane risk-of-bias tool, all trials had a high risk of performance bias due to the impossibility of blinding participants and personnel in lifestyle intervention trials and 8/28 RCTs had at least one additional area of high risk of bias (▶ **Fig. 2**).

Synthesis of the results

In total, 19/28 RCTs examined the rates of HDP after physical activity (4/19), diet (4/19) or combined interventions (11/19) (▶ **Table 2**/▶ **Fig. 3**). We pooled the Data presented using Mantel Haenszel method. Utilizing the Inverse Variance instead in the presence of high heterogeneity did not noteworthy change any results.

Among the **primary outcomes**, only exercise significantly reduced HDP was in the total group: OR 0.52 (95 % CI 0.28 to 0.96), but not in the meta-analyses of only pre-registered or audited RCTs (▶ **Fig. 3**, ▶ **Table 2**). Neither dietary interventions nor the combined approach significantly lowered HDP in any meta-analysis. Heterogeneity for HDP was moderate to high among all interventions. Sensitivity analysis showed a benefit of reduced rates of HDP if women participated in exercise sessions at least bi-weekly, as demonstrated in three RCTs: OR 0.45 (95% CI 0.20 to 0.99) [30, 31, 32].

All trials except for one trial investigated GDM (▶ **Table 2**) [37]. Although five singular RCTs achieved a significant reduction of GDM [30, 38, 39, 41, 44], this did not contribute to a significant reduction in any of our three meta-analyses. Heterogeneity for GDM was highest among interventions with only dietary or exercise (n = 7, I^2 = 69%, p < 0.01, respectively n = 9, I^2 = 59%, p = 0.01). Combined physical and dietary interventions (n = 15, I^2 = 41%, p = 0.05) had the lowest heterogeneity when they were supported by behavioral therapy (n = 5, I^2 = 0%, p = 0.48).

Only 6/28 RCTs provided data on perinatal mortality, and only 8/28 assessed if a newborn was admitted to a NICU (▶ **Table 2**). Thereby, Dodd et al. reported the number of children admitted to a NICU and a special care baby unit [43]. Both of those primary neonatal outcomes were too rare to calculate associations with singular interventions, and the effect of combined interventions was not significant. Statistical heterogeneity was low for combined interventions and both outcomes (perinatal mortality: n = 5, I^2 = 0 %, p = 0.50; NICU admission: n = 5, I^2 = 0 %, p = 0.54).

▶**Table 2 Primary Outcomes.** OR (odds ratios) with 95 % CI (confidence intervals) provided for primary outcomes within the total number of RCTs (randomized controlled trials, n = 28) as compared to a specified selection of either pre-registered or audited trials.

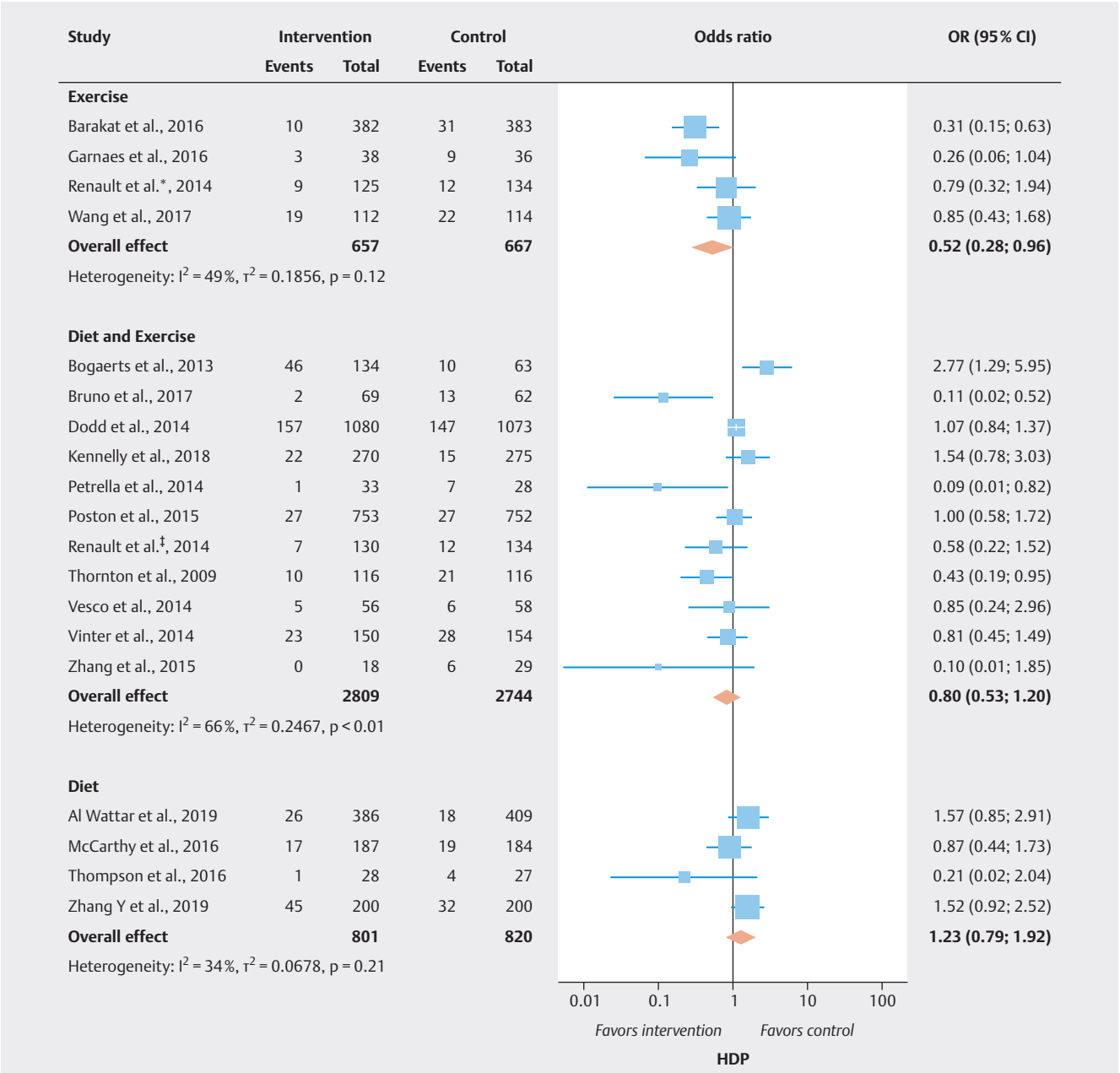
		All trials				Only pre-registered trials				Only audited trials			
Outcome	**Inter-vention**	**OR**	**95 % CI**	**n**	**I^2(%)**	**OR**	**95 % CI**	**n**	**I^2(%)**	**OR**	**95 % CI**	**n**	**I^2(%)**
GDM	Exercise	0.83	0.51–1.36	9	59	0.83	0.45–1.53	5	59	0.63	0.39–1.01	6	33
	Diet	0.87	0.55–1.39	6	69	1.02	0.61–1.70	4	65	0.93	0.65–1.35	4	55
	Diet and Exercise	0.83	0.66–1.03	15	41	1.06	0.91–1.23	8	0	0.87	0.68–1.10	12	45
	Subgroup: Behavioral therapy	0.91	0.75–1.11	5	0	0.95	0.78–1.17	4	0	0.95	0.78–1.17	4	0
HDP	Exercise	**0.52**	**0.28–0.96**	**4**	**49**	0.55	0.18–1.71	2	56	0.69	0.39–1.22	3	15
	Diet	1.23	0.79–1.92	4	34	1.40	0.83–2.35	3	30	1.34	0.95–1.89	3	1
	Diet and Exercise	0.80	0.53–1.20	11	66	1.06	0.87–1.29	5	0	0.75	0.51–1.10	9	60
	Subgroup: Behavioral therapy	1.08	0.75–1.57	4	0	1.14	0.76–1.71	3	0	1.14	0.76–1.71	3	0
NICU Admission	Exercise	0.56	0.19–1.64	2	0	0.56	0.19–1.64	2	0	NA	NA	1	NA
	Diet	NA	NA	1	NA	NA	NA	1	NA	NA	NA	1	NA
	Diet and Exercise	1.04	0.89–1.22	5	0	1.04	0.88–1.24	4	2	1.04	0.89–1.22	5	0
	Subgroup: Behavioral therapy	0.82	0.22–3.09	2	62	0.82	0.22–3.09	2	62	0.82	0.22–3.09	2	62
Perinatal mortality	Exercise	NA	NA	1	NA	NA	NA	0	NA	NA	NA	1	NA
	Diet	NA	NA	0	NA	NA	NA	0	NA	NA	NA	0	NA
	Diet and Exercise	1.00	0.54–1.86	5	0	1.07	0.57–2.02	4	0	1.00	0.54–1.86	5	0
	Subgroup: Behavioral therapy	1.11	0.23–5.13	2	31	1.11	0.23–5.13	2	31	1.11	0.23–5.13	2	31

GDM = gestational diabetes mellitus; HDP = hypertensive disorders in pregnancy; NA = not applicable; NICU = neonatal intensive care unit; significant results are printed in boldface

Among the **secondary outcomes** (▶**Table 3**), 23/28 RCTs analyzed absolute GWG. Whereas exercise significantly reduced maternal GWG in the total group: SMD −0.18 (95% CI −0.33 to −0.02) dietary interventions had only a significant effect on GWG in the specified meta-analyses with either pre-registered or audited trials: SMD −0.21 (95% CI −0.38 to −0.05), but not in the total group. Combined interventions significantly reduced the absolute GWG in the total group: SMD −0.38 (95% CI −0.57 to −0.20) and also in both specified meta-analyses whereby heterogeneity was high. Similarly, the rates of women with excessive GWG according to IOM criteria were significantly lower after exercise: OR 0.67 (95% CI 0.48 to 0.94) and after combined interventions: OR 0.48 (95% CI 0.30 to 0.74) as compared with controls. The effect was stronger in both specified meta-analyses and when adding behavioral therapy (▶**Table 3**). Heterogeneity was high for all interventions.

22/28 RCTs analyzed birthweight; it was only significantly reduced in all three meta-analyses when behavioral therapy supported combined interventions; all results showed a low heterogeneity (n = 4, I^2 = 0 %, p = 0.79). However, low birthweight is not only caused by the absence of macrosomia but can also be caused by a higher percentage of intrauterine growth retardation or pre-

▶ **Fig. 2** Application of the Cochrane Risk of Bias tool. Two independent reviewers classified the risk of each item among the singular trials (**a**) and in total (**b**) as either low (+), unclear (?) or high (−).



▶ **Fig. 3** Forest plot illustrating the effect of exercise, diet and combined interventions on hypertensive disorders in pregnancy (HDP). Squares indicate the odds ratios (OR) for the single studies; horizontal lines indicate 95% confidence intervals (CI). Diamonds indicate the overall effect (odds ratio and 95% confidence interval) for each intervention category and in total. If a trial compared more than one intervention arm, each arm was listed separately: * Exercise arm, ‡ Diet and Exercise arm.

maturity. Nevertheless, there were no associations between any intervention and the rates of preterm birth, LGA or SGA.

We performed meta-regression for primary and secondary outcomes within all three meta-analyses. There was no linear relationship between any intervention and potential effect modifiers. Excluding trials with a high risk of bias did not lead to relevant changes and funnel plots did not indicate any publication bias. Although literature supports higher maternal and fetal mortality associated with class three obesity in comparison to overweight or class one obesity, subgroup analyses by maternal pre-pregnancy BMI were not performed due to the limited availability of data [1].

▶**Table 3 Secondary Outcomes.** OR (odds ratios), respectively SMD (standardized mean differences) with 95 % CI (confidence intervals) are provided for secondary outcomes within the total number of RCTs (randomized controlled trials) (n = 28) as compared to the specified selection of either pre-registered or audited trials.

		All trials				Only pre-registered trials				Only audited trials			
Outcome	**Inter-vention**	**OR/ SMD**	**95 % CI**	**n**	**I^2 (%)**	**OR/ SMD**	**95 % CI**	**n**	**I^2 (%)**	**OR/ SMD**	**95 % CI**	**n**	**I^2 (%)**
Maternal													
Caesarean delivery	Exercise	0.96	0.75–1.22	5	0	1.24	0.46–3.31	2	51	1.06	0.76–1.50	4	0
	Diet	0.82	0.40–1.68	3	77	0.68	0.12–3.98	2	77	1.00	0.51–1.99	2	82
	Diet and Exercise	0.93	0.78–1.11	12	44	1.01	0.87–1.18	6	25	0.96	0.80–1.16	10	45
	Subgroup: Behavioral therapy	0.97	0.81–1.15	4	0	0.98	0.82–1.17	3	0	0.98	0.82–1.17	3	0
Gestational weight gain	Exercise	**– 0.18**	**– 0.33– – 0.02**	**8**	**59**	– 0.21	– 0.58–0.15	4	76	– 0.14	– 0.43–0.14	5	75
	Diet	– 0.55	– 1.16–0.06	3	92	**– 0.21**	**– 0.38– – 0.05**	**2**	**0**	**– 0.21**	**– 0.38– – 0.05**	**2**	**0**
	Diet and Exercise	**– 0.38**	**– 0.57– – 0.20**	**12**	**89**	**– 0.31**	**– 0.47– – 0.15**	**8**	**81**	**– 0.38**	**– 0.57– – 0.19**	**11**	**90**
	Subgroup: Behavioral therapy	**– 0.40**	**– 0.62– – 0.18**	**5**	**79**	**– 0.39**	**– 0.64– – 0.13**	**4**	**82**	**– 0.39**	**– 0.64– – 0.13**	**4**	**82**
Excessive gestational weight gain (IOM recommen-dations)	Exercise	**0.67**	**0.48–0.94**	**5**	**42**	0.77	0.19–3.10	2	76	0.80	0.25–2.55	2	80
	Diet	NA	NA	0	NA	NA	NA	0	NA	NA	NA	0	NA
	Diet and Exercise	**0.48**	**0.30–0.74**	**7**	**86**	**0.52**	**0.31–0.85**	**5**	**86**	**0.46**	**0.28–0.76**	**6**	**88**
	Subgroup: Behavioral therapy	**0.42**	**0.21–0.85**	**3**	**75**	0.34	0.09–1.28	2	88	0.34	0.09–1.28	2	88
Fetal													
Large for gestational age (LGA)	Exercise	0.83	0.45–1.55	4	39	0.63	0.37–1.06	2	0	0.83	0.45–1.55	4	39
	Diet	NA	NA	1	NA	NA	NA	1	NA	NA	NA	1	NA
	Diet and Exercise	0.76	0.55–1.05	9	56	0.78	0.56–1.08	7	59	0.76	0.55–1.05	9	56
	Subgroup: Behavioral therapy	0.58	0.24–1.43	3	81	0.58	0.24–1.43	3	81	0.58	0.24–1.43	3	81
Small for gestational age (SGA)	Exercise	1.62	0.61–4.26	3	0	1.74	0.31–9.75	2	32	1.62	0.61–4.26	3	0
	Diet	0.97	0.36–2.64	2	66	0.97	0.36–2.64	2	66	0.97	0.36–2.64	2	66
	Diet and Exercise	1.21	0.92–1.59	7	0	1.17	0.88–1.56	5	0	1.21	0.92–1.59	7	0
	Subgroup: Behavioral therapy	1.26	0.90–1.75	3	0	1.26	0.90–1.75	3	0	1.26	0.90–1.75	3	0

▶Table 3 continued

		All trials				Only pre-registered trials				Only audited trials			
Outcome	**Inter-vention**	**OR/ SMD**	**95% CI**	**n**	**I^2 (%)**	**OR/ SMD**	**95% CI**	**n**	**I^2 (%)**	**OR/ SMD**	**95% CI**	**n**	**I^2 (%)**
Birthweight	Exercise	−0.04	−0.17–0.09	7	48	−0.16	−0.31–0.00	4	24	−0.08	−0.23–0.07	6	43
	Diet	0.28	−0.27–0.82	4	91	−0.02	−0.26–0.23	3	43	−0.03	−0.35–0.29	2	71
	Diet and Exercise	−0.05	−0.14–0.03	11	42	−0.04	−0.17–0.08	7	61	−0.05	−0.14–0.05	10	46
	Subgroup: Behavioral therapy	**−0.16**	**−0.28–−0.04**	**4**	**0**	**−0.16**	**−0.30–−0.03**	**3**	**0**	**−0.16**	**−0.30–−0.03**	**3**	**0**
Preterm birth below 37 completed weeks	Exercise	0.83	0.53–1.28	4	0	0.57	0.15–2.23	2	0	1.01	0.43–2.37	3	0
	Diet	0.77	0.41–1.45	2	0	NA	NA	1	NA	NA	NA	1	NA
	Diet and Exercise	0.70	0.48–1.02	7	7	0.77	0.42–1.42	4	26	0.70	0.48–1.02	7	7
	Subgroup: Behavioral therapy	3.92	0.63–24.36	2	0	3.92	0.63–24.36	2	0	3.92	0.63–24.36	2	0

BM = body mass index; IOM = Institute of Medicine, recommendations for weight gain in pregnancy; LGA = Large for gestational age, birthweight > 90th centile, SGA = Small for gestational age, birthweight < 10th centile; NA = not applicable; significant results are printed in boldface, birthweight was measured in gram, gestational weight gain was measured in kg

Conclusions

In this meta-analysis of stringently selected RCTs, we were unable to demonstrate a clear benefit of lifestyle interventions for overweight or obese pregnant women on conventional short-term outcomes defined as primary outcomes. Although exercise significantly reduced HDP in the total group, the effect was not significant in pre-registered or audited meta-analyses. Nevertheless, the sensitivity analysis indicated that higher frequencies of physical activity did matter.

At first glance, this meta-analysis showed that interventions hardly improved the conventional primary outcomes even when we separated audited and pre-registered RCTs. However, this meta-analysis demonstrated that behavioral support increased the rates of favorable secondary outcomes of mothers and newborns.

The strength of our study is that we tried to limit the bias from p-hacking as proposed by Prior et al. and from poor control and feedback (audit) [14]. It is obvious that it needs a clear communicative strategy of health care providers to convince pregnant women to realize lifestyle changes. Therefore, it is not surprising that the integration of behavioral therapy significantly improved the secondary outcomes maternal GWG and neonatal birthweight. We must admit that the separate analyses according to registration or audit did not (yet) reveal new insights as we had hoped.

There are also weaknesses in our study: Interventions that require encouragement and involvement of patients cannot be blinded. This might cause a risk of performance bias. Women who were allocated to the control groups might have also become motivated for lifestyle changes. Further limitations include high heterogeneity. Although we attempted to identify potential confounders, the differences in population and intervention characteristics between the RCTs might have contributed to the high heterogeneity. None of the RCTs included in this meta-analysis have exactly the same intervention, leading to imprecise results of head-to-head pooling of data. Our results were only evaluated for singleton pregnancies. Since the implications of overweight, obesity and GWG differ in twin pregnancies [56, 57], we regret that there is a lack of RCTs evaluating lifestyle interventions in multiple gestation.

Previous meta-analyses have analyzed the effects of lifestyle interventions in pregnant women with a high BMI. Du et al. (2019) defined GWG and GDM as primary outcomes which were significantly reduced by exercise [58]. Two meta-analyses by Magro-Malosso et al. (2017) investigated the effect of physical activity. RCTs were only included if participants performed physical training three to seven times per week for at least 30 minutes. Then, the rates of GDM, HDP, and preterm birth were significantly reduced supporting the findings from our sensitivity analysis that not only the audit itself but also the frequency of exercise matters [59, 60]. It may be insufficient to control the compliance of participants by pedometers or food records. Instead, interventions should invite pregnant women with a high BMI to scheduled exercise classes and offer psychological support.

Retrospectively, perinatal mortality and NICU admission, which are typical characteristics of studies on preterm birth, were too rare in this Western cohort of women with a high BMI to calculate noteworthy effects of lifestyle interventions.

Maternal GWG and neonatal birthweight had originally been defined as secondary outcomes, which are less worrying for parents and their health care providers than our primary outcomes perinatal death or NICU admission which occur too rarely to show differences. However, GWG and birthweight are relevant because they are linked to the long-term health of mothers and their offspring as investigated by the developmental origins of health and disease concepts [61, 62, 63].

In opposite to communicable diseases, non-communicable diseases transmit epigenetically to second and third generations. However, lowering risks of maternal GDM and HDP alone does not seem to have a direct impact on childhood obesity [64]. The programmed life trajectories determine – together with genetics and life challenges – the ultimate cognitive outcomes and life quality [65]. Preventing obesity during pregnancy might have a lower effect compared to earlier interventions during childhood or preconceptionally to break the vicious circle of an epigenetic transgenerational passage of non-communicable diseases. Unfortunately, two recent meta-analysis could not show any effect of prenatal lifestyle interventions on childhood weight or growth [66, 67].

Secondary analyses of the DALY study have shown that sedentary behavior increases the concentration of cord blood leptin and neonatal body fat percentage, body fat mass and the sum of the skin folds associated with a risk of adiposity in childhood [68]. Since these risks are most likely increased in overweight and obese pregnant women who generally move less, lifestyle interventions should especially consider these target groups.

Up to now, there is only a small number of RCTs providing data on long-term follow up after lifestyle interventions during pregnancy: Anthropometric variables of children of mothers assigned to the “LIFE-Moms”-RCT were measured at one year post-partum whereas data of infants of the “LIMIT”-RCT were collected at three to five years of age [69, 70]. Both studies did not find relevant improvements in childhood adiposity. Long-term data from the second generation of the HAPO study are in progress [71]. Recently, analyses of fetal cord blood samples of participants of the TOP study showed that a diet and exercise-based lifestyle intervention for obese women altered epigenetic processes associated with offspring adiposity [72]. Research should be directed to intensify innovative solutions of programs with enduring effects. Future trials may also focus on pro-inflammatory, metabolic markers and epigenetic processes as described in the secondary analyses of the DALY group and the TOP-Study and use perinatal registers and research networks for follow-up [68, 72, 73].

Possibly, traditional lifestyle interventions should be replaced by creative concepts designed for the specific needs of pregnant women. Fact boxes and icon arrays may be used to better transmit evidence-based information [74]. Smartphone applications can support women to realize a healthy lifestyle [75]. Only then, we have a chance to respond to the individually varying etiologic aspects within the whole target group of overweight and obese pregnant women [76]. Together with the Foundation of the Berlin Philharmonic orchestra, recently, a study was launched using music within regular workshops and concerts for pregnant women to stimulate them to daily dance and move with classical music [77, 78].

Pregnancy is still an underutilized window of opportunity to improve long-term maternal and infant health [79]. The fact that the most robust strategies within our meta-analyses were a combination of lifestyle interventions with behavioral therapy, underlines that maternal obesity is a complex syndrome requiring dietary, physical activity and psychological support.

Overweight and obese women need more than average care or simple lifestyle advice. Instead, behavioral support combined with lifestyle interventions might better prevent adverse effects of maternal obesity. Perinatal care for overweight and obese women should also support increased intensities of physical activity.

Independently, pre-conceptional health education of adolescents and young women is required and modern media may be involved in the orchestration of researchers, health care providers, and health care politicians to intensify and audit these strategies [80, 81]. Long-term data of mothers and their offspring are future challenges after lifestyle interventions which may ideally start during childhood, are continued during adolescence and still supported during pregnancy and post-partum [82] .Only then, there will be a lifelong effect limiting the transgenerational passage of non-communicable diseases.

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Clinical Trial

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Conflict of Interest

The authors declare that they have no conflict of interest.

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