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Review

The influence of fasting and energy restricting diets on IGF-1 levels in humans: A systematic review and meta-analysis

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ABSTRACT

Background: Fasting and energy restricting diets have a potential means of delaying or preventing the onset of a range of age-related metabolic and neoplastic diseases. Consistently at the centre of this effect appears to be a significant reduction in circulating IGF-1 levels. The aim of the current systematic review and meta-analysis was to determine the influence of fasting and energy restriction on IGF-1 levels in human subjects.

Methods: A comprehensive systematic search was conducted from onset of the database to February 2019 in Embase, MEDLINE/PubMed, and SCOPUS to identify randomized clinical trials that investigating the impact of fasting or energy restriction circulating IGF-1 levels. Effect size was reported as weighted mean difference (WMD) and 95% confidence intervals (CI) using a random-effects models. Subgroup analysis was performed to identify the probable source of heterogeneity among trials.

Results: Total pooling of fasting and energy restriction randomised controlled trials in WMD analysis revealed no significant effect on circulating IGF-1 levels (WMD: −16.41 ng/ml, 95% CI: −35.88, 3.07). Sub grouped analysis fasting regimens appeared to substantially reduce IGF-1 (WMD: -28.87 ng/ml, 95% CI: −43.69, −14.05, I^2 = 00%), energy restricting regimens failed to do the same (WMD: -10.98 ng/ml, 95% CI: −33.08, 11.11, I^2 = 90%). Within this final subgrouping, it was observed that only energy restriction regimens of 50% or greater of normal daily energy intake were capable of significantly reducing IGF-1 levels (WMD: -36.57 ng/ml, 95% CI: −59.19, −13.95, I^2 = 00%). Finally, a meta regression were noted in which the percentage restriction of daily energy intake inversely correlated with plasma IGF-1 levels (p = 0.04).

Conclusion: This study uncovered that fasting significantly reduced levels of IGF-1, while energy restriction diets were successful only when intake was reduced by 50% or more.

1. Introduction

The growth hormone and insulin-like growth factor-1 (GH/IGF-1) axis is a well-conserved endocrine system that regulates organismal size as well as lifespan (Fontana et al., 2010). IGF-1 is an anabolic hormone mainly synthesized in the liver and locally expressed in peripheral tissues under the control of pituitary GH, within a negative feedback loop system (Sherlock and Toogood, 2007). GH/IGF-1 signalling is a requisite for normal growth in youth and for the maintenance of anabolic processes in adults (Sherlock and Toogood, 2007). IGF-1 bioactivity and bioavailability are purportedly influenced by six binding proteins (IGFBPs) (Lee et al., 1997). The most abundant binding protein

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Table 1
Baseline Characteristics of Included Studies in the Meta-analysis.

Studies	Author	Country	Year	Type of diet	Patients (n)	Percent of energy intake (from daily required energy intake)	Gender (1: female, 2: male, 3: both)	Attrition rate (intervention /control)	Adverse events
1	Kessler, C. S.	Germany	2018	Fasting	33	fasting	3	2/1	Headache, migraine, nausea, ravenousness, circulatory disturbance, hunger, general feeling of weakness, tiredness, stomach ache, meteorism, heartburn, and cold sensations in the body. Overall, the intervention was considered safe.
2	Wei, M.	USA	2017	Fasting mimicking diet	82	fasting mimicking diet	3	13/5	Fatigue, weakness, and headaches. Overall, the intervention was considered safe.
3	Papageorgiou, M.	UK	2017	Restricted	11	33	1	Non-reported	Non-reported
	Papageorgiou, M.	UK	2017	Restricted	11	33	2	Non-reported	Non-reported
4	Barnosky, A.	USA	2017	Restricted	41	75	3	11/14	Non-reported
5	Moro, T.	Italy	2016	Fasting	34	fasting	2	0/0	Non-reported
6	Koehler, K.	Germany	2016	Restricted	6	37	2	0/0	Non-reported
7	Fontana, L.	USA	2008	Restricted	28	80	3	0/0	Non-reported
8	Tam, Ch	USA	2014	Restricted	22	75	3	0/0	Non-reported
9	Fontana, L.	USA	2016	Restricted	188	75	3	26/14	Non-reported
10	Smith, W Jackson	USA	1995	Restricted	16	50	3	Non-reported	Non-reported

in serum is IGFBP-3, which is a circulating IGF-1 reservoir with potential IGF-1-independent cell survival and proliferative effects (Franklin et al., 2003). During the process of aging there is a gradual decrement and alteration in the pattern and production of GH secretion and IGF-1, respectively. This phenomenon, coined 'somatopause' (Muller et al., 1993), is considered to contribute to a relative anabolic hormone deficiency in the elderly. The somatopause is associated with alterations in body composition and metabolism and is comparable to those observed in adults with GH deficiency. This primarily manifests as a reduction of bone and muscle mass and strength, increased fat mass, dyslipidaemia, arterial hypertension, cardiovascular diseases, and cognitive decline (De Marinis et al., 2002). The impaired activity of the GH/IGF-1 axis could, putatively, be the basis of the numerous metabolic, biochemical, and functional alterations that characterize aging and disease (Muller et al., 1993).

Studies have reported that higher IGF-1 bioactivity may be correlated to an increased risk of several cancer types, including prostate (Renehan et al., 2004; Travis et al., 2016), colorectal (Kaaks et al., 2000), and premenopausal breast cancers (Sugumar et al., 2004). Given the potential opposing roles of the IGF-1 axis on overall markers of health and co-morbidities, a concerted effort is required to better understand the determinants of IGF-1 bioactivity. To that end, contemporary work has focussed on the influence of dietary alterations, and in particular, over or under-consumption (*i.e.,* fasting). Over-consumption of food is well known to manifest into metabolic co-morbidities (*e.g.*, insulin resistance, excessive accumulation of visceral fat, *etc.*), particularly when in combination with a sedentary lifestyle. Historically, animals, including humans, evolved in environments where food supply went through periods of relative scarcity. In turn, they developed numerous adaptations that permitted them to function, both physically and cognitively, when in a calorie deprived/fasted state. Intermittent fasting encompasses patterns of consumption in which individuals go extended periods of time (e.g., 16–48 h) with little or no energy intake, with intervening periods of normal food intake, on a recurring basis (Mattson et al., 2017).

Studies of laboratory animals have elucidated the cellular and molecular mechanisms by which individuals respond to fasting can increase overall fitness, and resistance to injury and a plethora of diseases (Longo and Mattson, 2014). In laboratory rodents periodic and intermittent fasting has resulted in profound beneficial effects on health and, notably, can counteract disease onset and improve functional outcome in experimental models of a wide range of disorders including diabetes, cardiovascular disease, cancers and neurological disorders such as Alzheimer's disease, dementia, Parkinson's disease and stroke (Mattson et al., 2017).

Given these promising results found in animal experimental models, the transferability of such findings into humans is of paramount interest. Recent randomized controlled trials in humans have demonstrated that intermittent fasting, including diets that mimic some aspects of fasting, are achievable and sustainable in humans, conferring numerous improvements of health indicators in healthy individuals, as well as some with chronic diseases. In studies administering intermittent fasting (e.g., 60% energy restriction on two days per week or every other day), periodic fasting (e.g., a five day diet providing 750–1100 kilocalories (kcal)) or time-restricted feeding (limiting the daily period of food intake to 8 h or less) in normal and overweight human participants, efficacy for weight loss and improvements across multiple health indicators including insulin resistance and reductions in cardiovascular risk factors has repeatedly been shown (Hill et al., 1989). The cellular and molecular mechanisms by which fasting may improve health and attenuates disease processes appears to rely on activation of adaptive cellular stress response signalling pathways which augments mitochondrial health, DNA repair and autophagy. Moreover, fasting may also promote stem cell-based regeneration, as well as continuing metabolic effects (Mattson et al., 2017).

IGF-1 has strong relationships with cancer risk, aging, diabetes and

innumerable other non-communicable diseases (Hursting et al., 2012; Wei et al., 2016). Although mechanistically speculative, there may be scope for easily-administrable fasting or dietary restriction regimens to positively influence IGF-1 levels. Therefore, it is of importance that relevant findings to-date be compiled and assessed. We, therefore, sought to systematically review and meta-analyse the influence of fasting and energy restriction on IGF-1 levels in human subjects.

2. Methods

2.1. Study design and search strategy

This systematic review and meta-analysis was performed according to the PRISMA [Preferred Reporting Items for Systematic Review and Meta-analysis] Statements (Moher et al., 2015). A comprehensive systematic search was conducted in Embase, PubMed/MEDLINE, and SCOPUS by two independent reviewers (JR and HKV) from inception until February 2019. We considered randomized Control Trials (RCTs) that evaluating the effects of fasting or/and energy restriction on circulating IGF-1 levels. Search strategy details were reported in Supplementary Table 1. Search strategy was developed without using date or language restrictions.

2.2. Selection criteria

The participant, intervention, comparison, outcome, time, and study design (PICOTS) criteria was used to establish study inclusion criteria. Endnote Reference Manager X8© was used for citation management. Duplicates were excluded using the Endnote function “remove duplicates”. Two independent authors (JR and HKV) investigated the abstract of all articles to select eligible studies and they reviewed the full-texts of relevant articles too. The following inclusion criteria were used: 1. Studies that have randomized controlled trial (RCT) design; 2. Studies on adult patients (age > 18 years); 3. Studies reporting results in the form of mean differences (MD) with the 95% confidence intervals (95% CI). Exclusion criteria were: 1. Studies not reporting IGF-1 levels before and after intervention; 2. Animal studies; 3. Non-randomised study designs; 4. Designs without a control group; 5. Conference abstracts, commentaries, case-reports, reviews.

2.3. Data extraction

One reviewer (JR) extracted the data, which was subsequently double checked by an additional reviewer (HKV). The data extracted included author, country, year of publication, duration of follow up, number of patients in intervention and control group, mean age (years), percent of energy restriction, and mean differences/standard deviation (SD) of IGF-1 levels in baseline study and post-intervention.

2.4. Quality assessment

Risk of bias assessment was applied to all included studies using the Cochrane collaboration’s tool for quality assessment of randomized control trials (Higgins et al., 2011), which contains the following domains: selection bias (random sequence generation), selection bias (allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other sources of bias.

2.5. Epidemiological cohort study

In order to confirm the findings in this meta-analysis of RCTs, we also examined the results of a population-based cohort study. The third national health and nutrition examination survey (NHANES III) data were used to investigate the relationship between daily energy intake and IGF-1 (35, 36). In NHANES III study, daily energy intake and IGF-1 levels were evaluated via 24 h recall and ELISA, respectively. Participants whose total daily energy intake was outside of the credible range (men < 800 or > 4200 kcal/day, women < 600 or > 3500 kcal/day) were excluded (37, 38). In the present study, we excluded participants with missing data in age, gender, IGF-1 levels, or daily energy intake. Furthermore, participants with cancer or diabetes were excluded from analyses.

2.6. Statistical analysis

Weighted mean difference (WMD) with the 95% CI were used for examination of effects of fasting or energy restriction on circulating IGF-1 levels. When the standard error (SE) of the mean difference for studies was reported, we calculated the SD using the following formula: SD^2 baseline + SD^2 final – (2 R* SD baseline + SD final) (Borenstein et al., 2009). Pooled WMD from included studies was calculated with derSimonian and Laird random-effects model. Heterogeneity across included studies was assessed using the Q-test, the I-squared and an alpha of 0.05 for statistical significance. Subgroup analysis was performed to identify the source of heterogeneity among trials. Type of intervention (fasting or energy restriction) and percent of energy restriction (less than 50% or more than 50% daily requirement energy intake) were considered as predefined source of heterogeneity. The potential effects of energy restriction were examined using fractional polynomial modelling in dose-response analysis and meta-regression analysis. The publication bias was determined using Egger’s, Begg’s tests and funnel plot. All statistical tests were conducted using the STATA 14 (StataCorp LP, College Station, USA), using a p value of 0.05 for statistical significance. One-way ANOVA was used to compare IGF-1 categories and daily energy intake(kcal/d) in men and women.

3. Results

Primary systematic search identified 3190 studies from PubMed/MEDLINE, Scopus, and Embase (Supplementary Fig. S1). Duplicate studies were removed and 1959 studies remained. During the primary screening, which was based on review of study titles and abstracts, 1925 studies were excluded and 34 studies remained for full text extraction. During secondary screening, 24 studies were excluded for the following reasons: 1) non-RCT design (n = 5), 2) and non-human trials (n = 19). Ten studies (eleven arms) containing 497 participants were included in the quantitative meta-analysis (Barnosky et al., 2017; Brandhorst et al., 2015; Fontana et al., 2016, 2008; Kessler et al., 2018; Koehler et al., 2016; Moro et al., 2016; Papageorgiou et al., 2017; Smith et al., 1995; Tam et al., 2014; Wei et al., 2017). One article from included studies had two arms, one arm for men and another arm for women(Papageorgiou et al., 2017).

3.1. Study characteristics

Characteristics of the included studies are detailed in Table 1. Six studies were conducted in US (Fontana et al., 2016, 2008; Papageorgiou et al., 2017; Smith et al., 1995; Tam et al., 2014; Wei et al., 2017), two in Germany (Kessler et al., 2018; Koehler et al., 2016), one in the UK (Papageorgiou et al., 2017), and one in Italy (Moro et al., 2016). All studies were published between the years 1995–2018. Three studies investigated fasting effect (Kessler et al., 2018; Moro et al., 2016; Wei et al., 2017), while the remaining seven studies involved an energy restriction design (Barnosky et al., 2017; Fontana et al., 2016, 2008; Koehler et al., 2016; Papageorgiou et al., 2017; Smith et al., 1995; Tam et al., 2014). There were 281 and 216 participants in intervention and control groups, respectively. The mean duration of interventions was 20 weeks and the mean age of participant was 36 years old. All studies were randomized controlled clinical trials and three studies described a cross-over design (Koehler et al., 2016; Papageorgiou et al., 2017; Smith et al., 1995). Headache and weakness were minor adverse effects reported as a result of intervention.

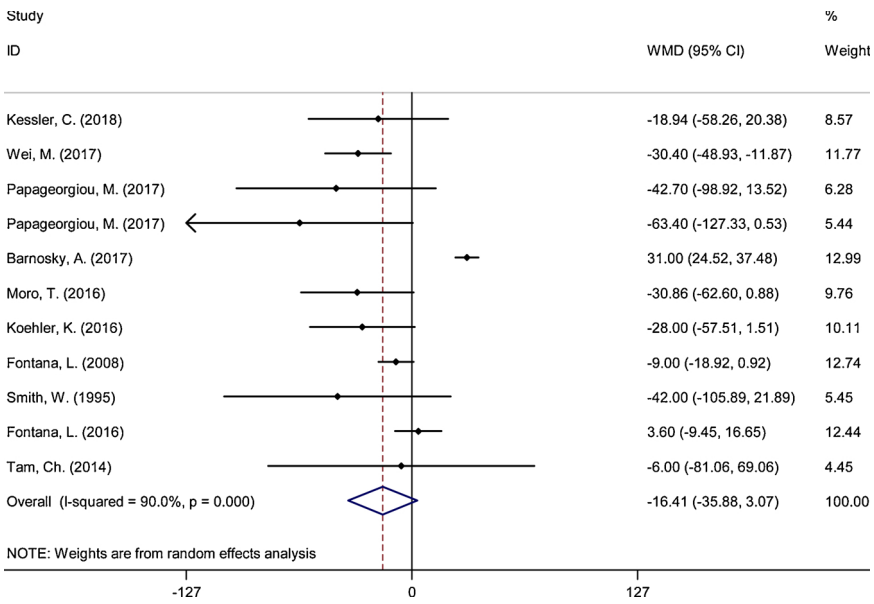


Fig. 1. Forest plot of randomized controlled trials investigating the effects of fasting and energy restriction on IGF-1 levels.

3.2. Meta-analysis results

Ten studies containing eleven arms providing a total of 472 participants reported changes in IGF-1 plasma levels as an outcome measure. Combined results using the random-effects model showed an overall insignificant reduction in IGF-1 following fasting or energy restricting (WMD: −16.41 ng/ml, 95% CI: −35.88, 3.07; Fig. 1). There was, however, a significant degree of heterogeneity among studies ($p = 0.001$, $I^2 = 90\%$).

3.3. Subgroup analysis

We subsequently stratified studies based on intervention type (Table 2). These analyses showed that fasting regimens (WMD: −28.87 ng/ml, 95% CI: −43.69, −14.05, $I^2 = 00\%$) more effectively reduced IGF-1 than energy restricting regimens (WMD: −10.98 ng/ml, 95% CI: −33.08, 11.11, $I^2 = 90\%$). However, a significant heterogeneity among energy restricting studies was also noted. In order to identify the source of this heterogeneity we, therefore, sub-grouped energy restricted studies based on percent of daily energy intake: those limiting to ≤50% normal required daily energy intake and those with limits > 50% normal required daily energy intake (Fig. 2). This analysis demonstrated that energy restriction significantly reduced IGF-1 levels when the energy intake is limited to 50% or less of normal required daily energy intake (WMD: −36.57 ng/ml, 95% CI: −59.19, −13.95, $I^2 = 00\%$).

3.4. Dose-response and meta regression

Seven studies containing eight arms demonstrated relation between energy restriction and changes in IGF-1 plasma levels (Barnosky et al., 2017; Fontana et al., 2016, 2008; Koehler et al., 2016; Papageorgiou et al., 2017; Smith et al., 1995; Tam et al., 2014). Subsequent analysis of the relationship between percentage of recommended daily energy intake and plasma IGF-1 alterations revealed a positive correlation (Coefficient for dose-response analysis = 1.0533, P for meta regression = 0.04; Fig.3). That is to say that the more substantial the calorie restriction, the greater the degree of circulating IGF-1 depletion.

3.5. Quality assessment

The results of the quality assessment of included studies is displayed in Table 3, where it was concluded that most studies had a high risk for bias. The risk of bias originated from the design of included studies; however, given the intervention of included studies was an energy restriction or fasting, studies could not reduce performance and detection bias, so, the likelihood results were adversely impacted is low.

3.6. Publication bias and sensitivity analysis

The Begg tests did not demonstrate significant publication bias between studies ($p = 0.45$), although Egger's test did report a significant publication bias between studies ($p = 0.01$) and asymmetry in the funnel plot is observed (Supplemental Fig. 2). We applied the 'trim and fill' method for adjusting for publication bias (Supplemental Table 2). The results of sensitivity analysis did not show any significant differences beyond the limits of 95% CI of calculated SESs for fasting or energy restricting intervention studies on IGF-1 (Supplemental Fig. 3).

3.7. Epidemiological cohort study

The study population contained 3394 participants (1496 men and 1898 women). Mean age of participants was 45 ± 17 years. Male and female participants with lower energy intake had significantly lower

Table 2
Results of subgroup analysis of included randomized controlled trials in meta-analysis.

Variables	Fasting	Energy restricted	All
IGF-1			
Number of studies	3	8	11
weighted mean difference (WMD) 95% CI	−28.87, −43.69, −14.05	−10.98, −33.08, 11.11	−16.41, −35.88, 3.07
I^2	00	90	90
p-heterogeneity	0.86	0.001	0.001

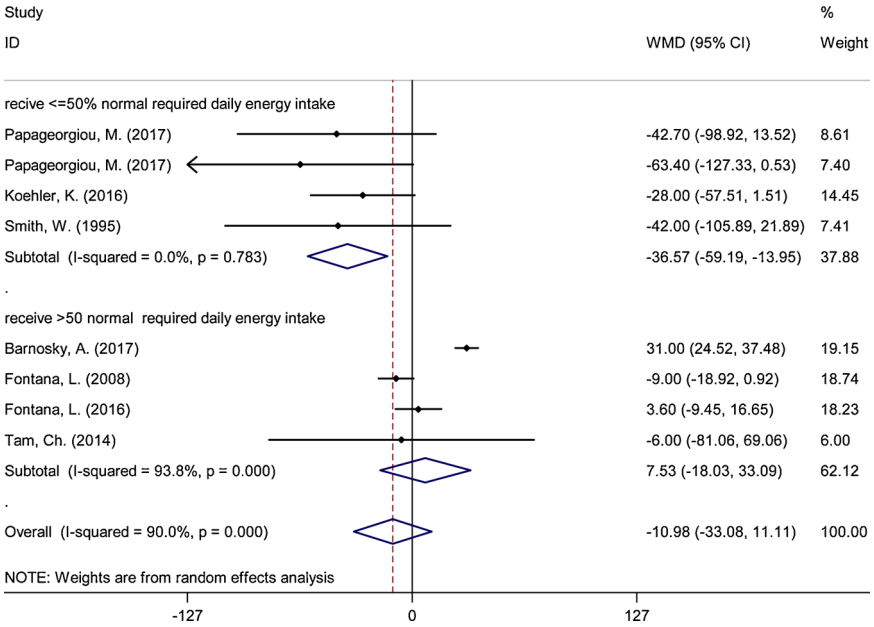


Fig. 2. Forest plot of randomized controlled trials investigating the effects of percent of energy restriction on IGF-1 levels.

IGF-1 levels when compared to those with high daily energy intake ($p < 0.001$ and $p < 0.001$, respectively; Fig. 4).

4. Discussion

Despite promising preclinical experimental evidence and clinical associations, the efficacy with which fasting or energy restriction protocols alter age-related health in humans remains contentious, and reliable clinical evidence has not been the subject of systematic scrutiny up to this point. For this reason, the current meta-analysis aimed to compile and interrogate the currently available data surrounding the effects of such regimens on plasma levels of IGF-1 in humans. In this study, we reviewed a total of ten RCTs containing 11 relevant arms: eight energy restriction and three fasting-type protocols. Overall, our research indicates that there was no effect of fasting regimens and energy restriction protocols when all arms were pooled. However, due to the significant degree of heterogeneity in this analysis, subgroup investigations were performed. The results demonstrate that fasting regimens and energy restriction protocols in which participants were limited to less than half of their required daily intake both resulted in significantly reduced levels of circulating IGF-1.

Fasting and energy restriction-based dieting has garnered significant attention in the past decade for purported beneficial effects on metabolic function and age-related parameters. In parallel, a number of epidemiological studies have identified associations between elevated circulating IGF-1 and aging or cancer progression (Cao et al., 2015; Kaaks et al., 2000; Renehan et al., 2004; Sugumar et al., 2004; Travis et al., 2016). For example, increased rates of gastrointestinal cancers are observed in acromegalic patients (Renehan et al., 2003), a cohort defined by inherently elevated levels of GH and IGF-1. In direct contrast, those individuals with hereditary IGF-1 deficiencies appear to enjoy vast protection from age-related cancers and diabetes (Guevara-Aguirre et al., 2011). In concert with this observational data, preclinical studies investigating the development of a plethora of age-related diseases (*i.e.*, cancers, diabetes, cardiovascular and neurodegenerative diseases) have repeatedly demonstrated a role of IGF-1 (Harvie et al., 2011). For example, a recent study of calorie restriction in non-human primates demonstrated a significant improvement in longevity and reduction in age-related disease (Mattison et al., 2017). In addition, extensive meta-analysis of 59 preclinical studies examining the effect of calorie restriction regimens on cancer development also reported a staggeringly reduced tumour incidence odds ratio of 0.20 across the models; although the propensity for intermittent fasting to achieve the same effect was deemed doubtful (Lv et al., 2014). The exact mechanisms through which fasting and energy restriction affect age-related disease remain incompletely elucidated; however, IGF-1 may play an important role in age-related disease (Castellino et al., 2018; Junnila et al., 2013; Lechler et al., 2017; Longo, 2019; Mattson et al., 2004) and could represent a novel target in the combatting such disorders.

The three studies assessing fasting-style regimens ultimately included in the present meta-analysis demonstrate a clear depletive effect of such protocols on circulating IGF-1, with little obvious heterogeneity between the study outcomes. However, the manner in which these studies were designed and executed differs somewhat. While two trials implemented an intermittent fasting regimen (Kessler et al., 2018; Moro et al., 2016), and the final study examined the effects of a 'fasting-mimicking' diet in which participants consumed a modified diet depleted in calories, carbohydrates and protein, but high in unsaturated fats (Wei et al., 2017). Although there is obvious discordance in the design of the latter study in relation to the two intermittent fasting studies, the positive effects certainly warrant further investigation and should be considered carefully.

The CALERIE-1 trial, in which participants undertook a continuous 25% reduction in energy intake for six months, found that subjects reduced their 10-year cardiovascular risk by a substantial 10% (Heilbronn et al., 2006; Lefevre et al., 2009; Redman et al., 2010). Despite this, no effect on circulating IGF-1 was recorded. The same can be said for the CALERIE-2 trial, in which an extended 2-year intervention of the same energy restriction regimen brought about a range of biophysical and biochemical alterations, including a rise in IGFBP-1, yet failed to yield reductions in circulating IGF-1 levels (Fontana et al., 2016). This has previously been attributed to the young age and healthy status of the study participants (Most et al., 2017); however, the analysis presented in the present study indicates that calories restriction of less than 50% is ineffective in reducing IGF-1. Moreover we demonstrate that IGF-1 alterations were dose-dependent in terms of response to percentage of daily energy intake restriction. In line with this, quartile grouping of men and women by their daily energy intake revealed significant trends, with the lowest energy intake quartiles demonstrating the lowest circulating IGF-1 levels in both men and women. With this in mind, future research may need to focus efforts and resources towards protocols with higher degrees of energy

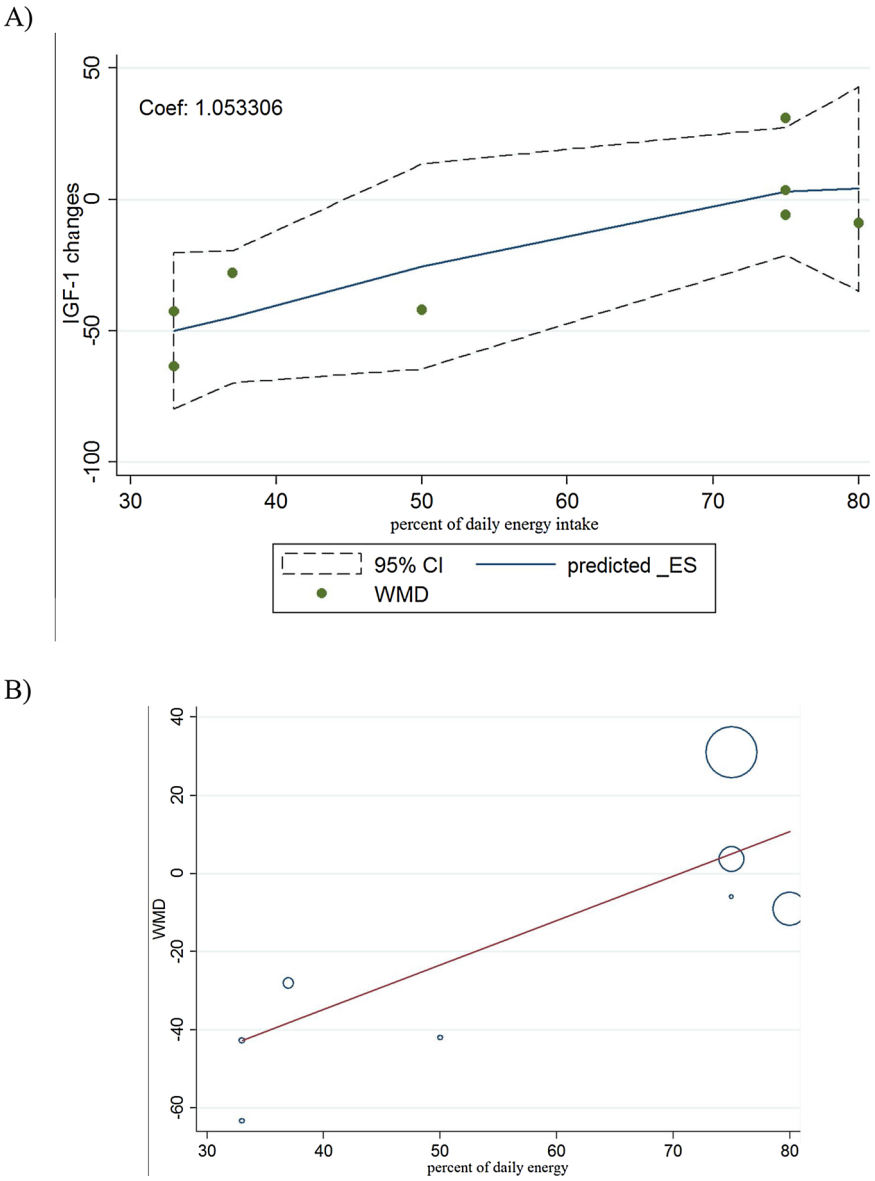


Fig. 3. A) Dose-response analysis - percent of normal daily required energy intake and IGF changes. Weighted mean difference, WMD., B) Meta regression analysis (percent of normal daily required energy intake and IGF changes).

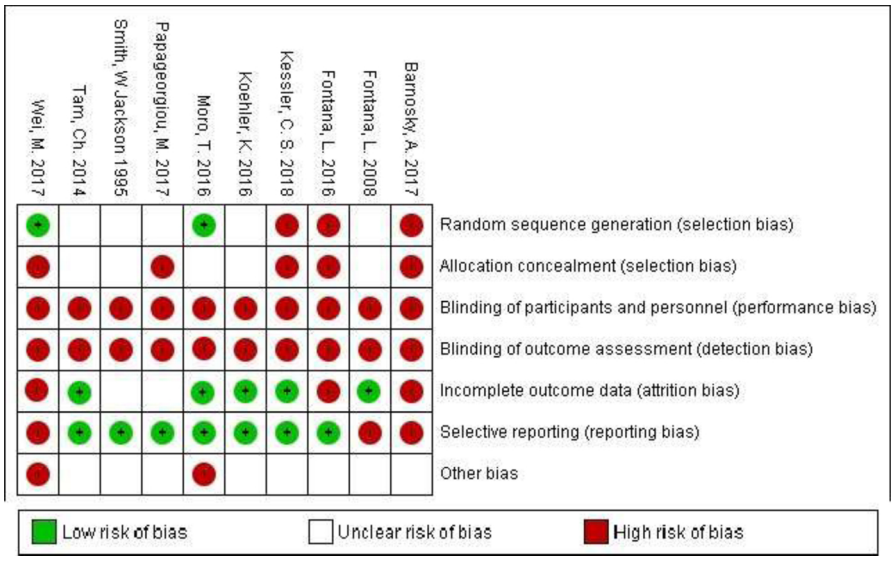
restriction, if we are to achieve IGF-1 depletion mediated effects.

Finally, although not directly assessed in the present analysis, it is worth considering that intervention duration may have a paradoxical effect on IGF-1 levels. That is to say that the human system may adapt to extended periods (*i.e.* years) of calorie restriction, resulting in insignificantly altered levels of plasma IGF-1. This was exemplified by Fontana and colleagues, as they demonstrated that a short-term 3-week calorie restriction, but not the extended 1 and 6-year interventions conferred a significant decrease in circulating IGF-1 (Fontana et al., 2008). In line with this, three of the arms analysed in this meta-analysis with the longest intervention durations were not found to display significantly reduced IGF-1 at study completion (Barnosky et al., 2017; Fontana et al., 2016; Tam et al., 2014). Therefore, we must ask the question: does the short-term effect of such regimens on IGF-1 concentration persist over time? This may be an important consideration for future research and should encourage trials to monitor IGF-1 in a kinetic manner over the course of intervention.

4.1. Limitations and strengths

There are several limitations of this study which are important to consider. The studies included in this meta-analysis all contained small and relatively heterogenous RCTs (n = 6-188), and just three studies assessed fasting-style regimens. In addition, there existed a substantial degree of heterogeneity in experimental design between studies, with a wide range of intervention durations and dietary intervention protocols. Finally, the studies included reported on a range of subject types, including obese, overweight and healthy-weight adults. It should be considered that these populations likely display differing levels of plasma IGF-1, although this issue is partially controlled for by considering alterations from baseline. In addition, despite these heterogeneities, the random-effects model methodology applied to the current study represents a significant design strength in further controlling for such factors. Interestingly, despite the high level of calorie restriction applied in the included studies, there were no major adverse events reported. Although, in some trials, authors reported a minimal number of participants lost to attrition, and in Table 1 we demonstrate that only two studies reported adverse effects attributable to intervention. In

Table 3
Risk of bias assessment.



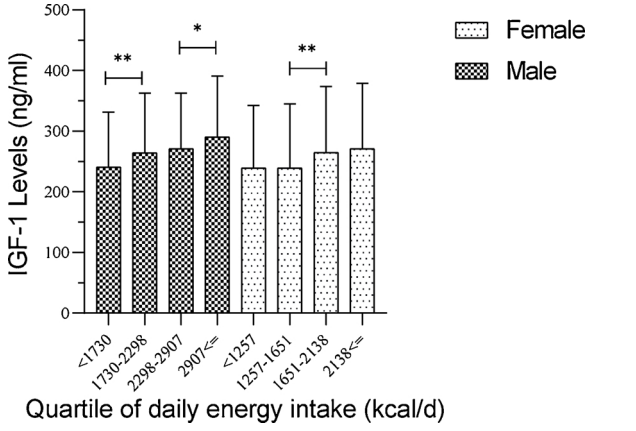


Fig. 4. Relation between Total energy intake and IGF-1 in male and female (*0.05, **0.01).

Kessler et al (2018), headache, migraine, nausea, ravenousness, circulatory disturbance, hunger, general feeling of weakness, tiredness, stomach ache, meteorism, heartburn, and cold sensations in the body. Similarly, in Wei et al (2016), fatigue, weakness, and headaches were reported. Moreover, two studies, Barnosky et al (2017) and Fontana et al (2016), reported that 11 and 26 intervention group participants were lost to attrition, respectively; however, there were no adverse issues or events reported. In fact, in all included studies in this meta-analysis, the intervention was regarded as being safe. Promisingly, in some studies, for example, Brandhorst et al (2015), systematic evaluations of tolerability and perceived adverse events have been conducted; where only mild discomfort was reported, and most occurrent in the initial stages of prolonged fasting/calorie restriction, after which, participant reported adversity was lower, which could explain why Barnosky et al (2017) and Fontana et al (2016) had participants withdraw, but had no adverse events reported. Notwithstanding, caution must be taken with respect to the population/patient enrolled on such an extreme calorie restriction (50%), which could cause adverse effects, including the exacerbation of previous malnourishments and dysfunctions, particularly in old and frail participants. Thus, highlighting the need for detailed viability assessment and patient history documentation prior to enrolment on any fasting or calorie restricting diet. A further, potential limitation, and indeed avenue for further work, is that, due to a dearth of eligible studies, we could not evaluate macronutrient composition of diets, which may conceivably be of importance. It is possible that, independent of calories, a protein or carbohydrate restriction may have a different effect on IGF-1. For instance, it is recognized that protein deprivation is associated with lower IGF-1 concentrations in animals and malnourished children (Estívariz and Ziegler, 1997; Thissen et al., 1994; Underwood et al., 1994); whilst in healthy well-nourished men, greater dietary intake of protein is shown to be associated with higher IGF-1 concentrations (Larsson et al., 2005). On the other hand, intakes of total energy, alcohol, total fat, and carbohydrate are reportedly not associated with IGF-1 concentrations (Larsson et al., 2005). Thus, the authors advocate that further research manipulate and assess the composition and restriction of dietary macronutrients, and the subsequent impact of IGF-1.

5. Conclusions

The primary outcome of this study was that, when compiled, RCT studies assessing fasting and energy restricting diets did not elicit a significant effect on circulating IGF-1. However, subsequent subgroup analyses revealed that both fasting regimens and energy restriction to ≤50% normal required daily energy intake resulted in significantly reduced levels of plasma IGF-1 in human subjects. To the authors' knowledge, this study represents the first meta-analysis to investigate the effects of fasting and energy restricting regimens on circulating IGF-1 and should aid in directing future research in the area.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.100910.

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