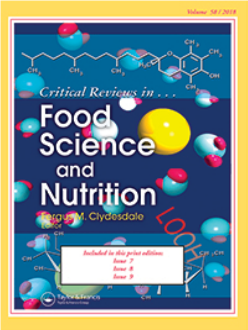

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The effect of vegetarian diets on iron status in adults: A systematic review and meta-analysis

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ABSTRACT

Background: Vegetarian diets exclude meat, seafood, and products containing these foods. Although the vegetarian lifestyle could lead to a better health status in adults, it may also bear risks for certain nutritional deficiencies. Cross-sectional studies and narrative reviews have shown that the iron status of vegetarians is compromised by the absence of highly bioavailable haem-iron in meatless diets and the inhibiting effect of certain components present in plant foods on non-haem iron bioavailability.

Methods: The databases Pubmed, Scopus, Embase, and Cochrane CentralRegister of Controlled Trials were searched for studies comparing serum ferritin, as the major laboratory parameter for iron status of adult vegetarians with non-vegetarian control groups. A qualitative review was conducted as well as an inverse-variance random-effects meta-analysis to pool available data. In addition the effect of vegetarian diets according to gender was investigated with a subgroup analysis. The results were validated using a sensitivity analysis.

Results: A total of 27 cross-sectional studies and three interventional studies were selected for the systematic review. The meta-analysis which combined data of 24 cross-sectional studies showed that adult vegetarians have significantly lower serum ferritin levels than their non-vegetarian controls (-29.71 μg/L, 95% CI [-39.69, -19.73], $p < 0.01$). Inclusion of semi-vegetarian diets did not change the results considerably (-23.27 μg/L, 95% CI [-29.77, -16.76], $p < 0.01$). The effects were more pronounced in men (-61.88 μg/L, 95% CI [-85.59, -38.17], $p < 0.01$) than in both premenopausal women (-17.70 μg/L, 95% CI [-29.80, -5.60], $p < 0.01$) and all women (-13.50 μg/L, 95% CI [-22.96, -4.04], $p < 0.01$), respectively.

Conclusions: In conclusion our results showed that vegetarians are more likely to have lower iron stores compared with non-vegetarians. However, since high iron stores are also a risk factor for certain non-communicable diseases, such as type 2 diabetes, it is recommended that not only vegetarians but also non-vegetarians should regularly control their iron status and improve their diet regarding the content and bioavailability of iron by consuming more plants and less meat.

KEYWORDS
Vegetarian diets; vegan diet; vegetarians; iron; iron status; ferritin; systematic review; meta-analysis

Introduction

A vegetarian is a person who does not eat meat, including poultry, fish, and seafood, or products containing these foods (Craig et al., 2009). Vegetarians are classified as lacto-ovo-vegetarians (LOV) if they avoid the flesh of animals but consume dairy, eggs, and other animal products. Lacto-vegetarians (LV) additionally exclude eggs from their diet, but include dairy, whereas ovo-vegetarians (OV) exclude dairy, but include eggs. The vegan (V) diet excludes all animal-derived foods (Phillips, 2005). Dietary patterns following a vegetarian lifestyle to a large extent but still including some forms of meat can be classified as demi- or semi-vegetarian (SV) (Craig et al., 2009; Phillips, 2005). Specific examples are pescetarianism, pollotarianism, and pollo-pescetarianism, which include only seafood, poultry, and white meat, respectively (Nordic Council of Ministers, 2014).

In contrast to these widely used definitions, other criteria have been used in research studies to describe forms of vegetarian diets. For example, participants described as LOV consumed poultry and fish less than once every 15 days (Meirelles et al., 2001), no more than once a week (Wilson and Ball, 1999), or any type of meat less than six times a year (Li et al., 2000).

Vegetarian and vegan diets have been shown to exert beneficial effects on multiple health outcomes, such as cancer and ischemic heart disease (Dinu et al., 2016). On the other hand a high intake of red meat is associated with an increased risk for especially type 2 diabetes and colorectal cancer (Ekmekcioglu et al., 2016) with high loads of haem-iron playing a mechanistical role (Ekmekcioglu et al., 2016). However, vegetarians are also at risk for a suboptimal supply with some nutrients including iron (Craig, 2010). Iron deficiency (ID) is the most common nutrient deficiency in the world with approximately 25% of the world population suffering from decreased iron stores (Cook, 1994; Miller, 2013). Physiological or primary ID develops when the bodily need

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for iron is not met by iron absorption from the diet (Killip et al., 2007). Serum ferritin (Fer) is the most effective parameter in the diagnosis of ID as well as iron overload (Polin et al., 2013). However, Fer acts as an acute phase protein and is increased in inflammatory and malignant diseases, possibly masking ID, which in this case may exist even with Fer values of up to 100 μg/L (Abbaspour et al., 2014; Bermejo and Garcia-Lopez, 2009; The Ontario Association of Medical Laboratories, 1995).

Many plant foods contain high amounts of iron, foremost legumes, beans, whole grains, and dark-green leafy vegetables (Lönnerdal, 2009). It is therefore possible to achieve a vegetarian diet with an iron content similar to meat-containing diets (Craig et al., 2009). Many large cohort studies even describe a higher intake in the vegetarian and especially vegan population (Cade et al., 2004; Clarys et al., 2014; Davey et al., 2003; Shridhar et al., 2014). However, the bioavailability of iron from meatless food is substantially lower than from diets including animal flesh, leading to a lower amount of absorbed iron (Hallberg et al., 1997; Hunt and Roughead, 1999). This is due to inhibiting factors, most of all phytic acid (Hallberg, 1981) but also polyphenols, such as tannic acid and chlorogenic acid in vegetables, fruit, some cereals and legumes, tea, coffee, and red wine (Hallberg, 1981). On the other hand, organic acids like ascorbic acid enhance the bioavailability of non-haem iron to some extent (Hunt, 2002; Sharp, 2010). It has been for example reported that the mean iron absorption from a vegetarian diet is 10% compared to 18% through a diet containing meat (Food and Nutrition Board and Institute of Medicine, 2001; Hunt, 2003).

Several cross-sectional studies have analysed the iron status, mainly as Fer levels, in vegetarians vs. non-vegetarians (NV). While some of them showed no statistically significant difference between the iron stores of vegetarians and NV (Deriemaeker et al., 2011; Harman and Parnell, 1998; Hunt and Roughead, 1999), others demonstrated significantly lower iron stores for vegetarians compared to NV (Harvey et al., 2005; Obeid et al., 2002; Yen et al., 2008). A few studies even reported a higher prevalence for ID and iron-deficiency anaemia (IDA) in vegetarians, especially in females (Bhatti et al., 2007; Kajanachumpol et al., 2011; Shaw et al., 1995).

Although the issue of iron status of vegetarians has been addressed by several original studies and few narrative reviews, no systematic review and meta-analysis has to our knowledge been carried out yet. Therefore, we conducted a systematic literature search to summarise and meta-analytically synthesize existing data in order to provide an up-to-date statement whether vegetarian diets significantly influence iron status parameters in otherwise healthy adults.

Methods

Protocol and registration

The study protocol for this systematic review and meta-analysis was registered with the international database for prospectively registered systematic reviews (PROSPERO) under the registration number CRD42013005822.

Search methods for identification of studies

Electronic searches

This systematic review was planned, conducted and reported in adherence with standards of quality for reporting meta-analyses (Moher et al., 2009).

A literature search was conducted using the databases Pubmed, Embase, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy to identify all studies examining parameters of iron metabolism and storage in vegetarians and matched omnivores was ("vegetarian" OR "vegan" OR "meatless") AND "ferritin." The search was carried out in Pubmed in "All fields," in Scopus in "Article title, Keyword, Abstract," in Embase in "Keywords," and in CENTRAL without restrictions. Results were limited to English and German studies. Studies published earlier than the year 1972 were excluded as Fer was not used as a parameter to estimate iron stores before then (Wang et al., 2010). Studies published later than the time of the literature search, i.e. July 12th, 2016, were also not included in the systematic review and meta-analysis.

Searching other resources

In addition, a hand search was performed to identify relevant studies in the references of all included studies and pertinent review articles. Unpublished and on-going trials were sought by searching a selection of national and international trial registries, which are listed in Table 1.

Criteria for considering studies for this review

Types of studies

Due to the form of intervention/exposure, i.e., vegetarian diets, the identification of blinded studies was not to be expected. However, these studies would have been included in the systematic review if they had been available. Non-blinded randomised controlled trials (RCT), case-control studies, and cohort studies were considered to be of appropriate validity for the systematic review. Cross-sectional studies were also included in the systematic review and meta-analysis although of a lower informative value. However, they form the largest part of the available evidence on iron status in vegetarians and matched omnivores and therefore contributed the most to this review.

Table 1. List of all trial registries used to identify unpublished data.

Trial registry	Website
The Australian New Zealand Clinical Trials Registry	www.anzctr.org.au/
ClinicalTrials.gov registry (U.S. National Institutes of Health)	www.clinicaltrials.gov/
Community Research & Development Information Service (European Union)	www.cordis.europa.eu/en/home.html
European Medicines Agency	www.clinicaltrialsregister.eu/ctr-search/search
The International Standard Randomised Controlled Trial Number Registry	www.isrctn.com/
University Hospital Medical Information Network Clinical Trials Registry (Japan)	www.umin.ac.jp/ctr/
WHO International Clinical Trials Registry Platform	www.who.int/trialsearch

Types of participants

Participants had to be at least 18 years of age due to the impact of growth spurts on iron stores. In trials including persons both older and younger than 18 years, data of eligible participants were used when they were clearly presented separately. Both genders were included and, where possible, analysed separately. Another aim was to differ between data for pre- and postmenopausal women, due to the effect of menstruation on iron stores. Data on pregnant and lactating women were excluded.

Participants with genetic disorders of iron storage and metabolism were also excluded. Diseases interfering with Fer levels, i.e. inflammatory, malignant, liver, and kidney diseases, malassimilation, and eating disorders, were other exclusion criteria. Studies researching groups of athletes, who have an unusually high need for iron and are suspected to suffer from diminished iron stores, were not included in this systematic review. Studies primarily investigating iron deficient or anaemic participants and studies listing ID or anaemia as exclusion criteria were excluded as well. Data of iron-supplement users were also not included in the systematic review and meta-analysis except for studies including equal percentages of iron supplement users in both diet groups and studies stating that results did not change after excluding iron supplement users.

Types of exposure

In this study, a LOV was defined as someone excluding all animal flesh, a LV and OV as someone additionally excluding egg products and dairy products, respectively, and a V as someone excluding all products of animal origin. Populations consuming any type of meat ≤ 1 per week were defined as SV and also included in the study. If no description of the type of vegetarian diet was available and no indication was given that meat might be consumed frequently, the group was classified as "vegetarian" (VEG) and included in the study. Other forms of vegetarianism, e.g., a macrobiotic diet or raw-foods diet, were not investigated. In cases where the definition of the vegetarian diet given by the study group deviated from these definitions the data were analysed according to the latter. Whenever data of two different groups of vegetarians were combined, the less restrictive definition was used. A minimum time period of following the vegetarian diet pattern was not defined, as there is no definite evidence available regarding the adaptation of iron stores to a new diet pattern.

Types of outcome measures

The primary outcome for investigating the iron status of vegetarians and matched omnivores was Fer, as it is the most valid indicator of iron stores (Polin et al., 2013). Studies were therefore only included in the systematic review if results on Fer were available.

Data collection and analysis

Selection of studies

After exclusion of duplicate studies, the abstracts of remaining studies were screened for eligibility by one review author (Haider). Uncertainties were resolved by discussion with a second review author (Ekmekcioglu). Full-text papers for all potentially relevant studies based on the review of abstracts were retrieved and analysed.

Authors of unpublished studies and studies published only as abstracts were contacted as well as authors of published studies missing essential information on study characteristics. The study was excluded if required data were not provided. The study selection process was documented in form of a flowchart.

Data extraction

Data on the characteristics of studies, including study type, participants, form of exposure, and results, was extracted from selected studies by one review author (Haider). Uncertainties were discussed with a second review author (Ekmekcioglu).

The study author was contacted if Fer levels were measured, but results were not presented in the study. Failure to provide any form of data led to the exclusion of the study. The author was also contacted if the results were presented using effect measures not compatible with meta-analyses, or if results were presented as diagrams or figures making it impossible to abstract the data for the meta-analysis. If no sufficient data was provided, the study was used only in the systematic review but not the meta-analysis.

Assessment of risk of bias in selected studies

An abundance of tools for the evaluation of RCTs exist, whereas only few tools assess the quality of case-control studies and cohort studies and no universally accepted risk assessment tool for cross-sectional studies is available up until now (Zeng et al., 2015). The tool most valid to evaluate the risk of bias and quality of selected RCTs was considered to be the Risk of Bias Assessment Tool by the Cochrane Collaboration (Higgins and Green, 2011. Available from www.cochrane-handbook.org). Non-randomised interventional studies were evaluated using the Methodological Index for Non-Randomised Studies (MINORS) (Slim et al., 2003). Cohort studies and case-control studies would have been assessed using the Newcastle Ottawa Scale for observational studies (NOS) (Cook and Reed, 2015). Cross-sectional studies were evaluated using a checklist provided by the Agency for Healthcare Research and Quality (AHRQ) (Viswanathan et al., 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/).

The assessment was conducted by one review author (Haider) and uncertainties resolved by discussion with another review author (Schwingshackl).

The results were incorporated into the interpretation of results by excluding high-risk studies during the sensitivity analysis. In the case of cross-sectional studies, a points-based system was used: For each question of interest, one point was given if risk of bias was considered to be low, 0.5 points if it was deemed intermediate, and no points if risk of bias was high, leading to a maximum possible score of eight points for each study. The exact criteria for high, intermediate, or low risk of bias in cross-sectional studies are listed in Table S1. Studies with a score of less than five points were eliminated during the sensitivity analysis.

Measures of treatment effect

As all outcome measures of interest are continuous data, a well-known scale exists for results. Therefore, the effect measure of choice was the mean difference (MD). Due to the fact that cross-sectional studies do not allow for change scores, post-intervention values were used in all comparisons.

Unit of analysis issues

As none of the interventional studies was included in the meta-analysis, none of the techniques controlling for different study designs and differences in the presentation of results was necessary.

A relevant issue with some of the cross-sectional studies was the inclusion of more than one vegetarian and/or non-vegetarian group. Data was combined for these groups using the equation provided by the Cochrane Collaboration (Higgins and Green, 2011. Available from www.cochrane-handbook.org):

Equation 1: Combining data. M: mean, N: number of participants

$$\sqrt{\frac{(N1-1)^{*}SD1^{2}+(N2-1)^{*}SD2^{2}+\frac{N1^{*}N2}{N1+N2}^{*}(M1^{2}+M2^{2}-2^{*}M1^{*}M2)}{N1+N2-1}}$$

Dealing with missing data

Data presented as arithmetic mean and standard deviation (SD), standard error of the mean (SEM), or confidence intervals (CI) are compatible with meta-analyses and were included in this study without converting them to other outcome measures. Results presented as median and interquartile ranges (IQR) or median, minimum, and maximum were converted to mean and SD using distribution-free equations provided by Hozo et al. (Hozo et al., 2005) and Wan et al. (Wan et al., 2014). Data presented as geometric mean and CI were converted to arithmetic mean and SD using equations provided by Higgins et al. (Higgins et al., 2008).

Assessment of heterogeneity

Due to the widely varying definitions of the term "vegetarian" and differences in demographic characteristics the clinical heterogeneity of included studies was expected to be high. The methodological heterogeneity was not expected to vary considerably as standard techniques exist for the analysis of Fer levels. To assess the statistical heterogeneity, the chi-squared test was applied and the level of significance set at $p < 0.10$ for statistically significant heterogeneity. However, as this test has a low power for studies of small sample sizes, the inconsistency was primarily evaluated using I^2, which describes the percentage of total variation in effect estimates across studies that is due to heterogeneity rather than sampling error. An I^2 of 0–40%, 30–60%, 50–90%, and 75–100% may represent irrelevant, moderate, substantial, and considerable heterogeneity, respectively. (Higgins and Green, 2011. Available from www.cochrane-handbook.org)

Assessment of publication bias

Publication bias in this systematic review and meta-analysis was assessed via inspection of the funnel plot whenever more than ten studies were compared.

Data synthesis

For each outcome measure of interest, a random-effects inverse-variance meta-analysis was performed using the program Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The random-effects model was preferred to account for the heterogeneity in studies. Three comparisons were conducted for each outcome measure of interest where possible:

1. LOV+LV+OV+V vs. NV: The effect of a meatless diet compared to an omnivorous diet was investigated. Groups of defined LOV, LV, OV, and V were analysed together, as non-meat animal products do not contain higher amounts of bioavailable iron or iron inhibitors compared to plant foods.
2. LOV+LV+OV+V+VEG+SV vs. NV: The effect of a meatless or low-meat diet compared to a diet including meat more frequently was investigated.
3. SV vs. NV: The effect of a low-meat diet compared to a high-meat diet was investigated.

The results were presented in form of a forest plot for each analysis.

Subgroup analysis

A subgroup analysis was carried out to investigate the effect of gender on the outcome of the meta-analysis. Data for study groups including only men, only premenopausal women, only postmenopausal women, pre- and postmenopausal women, and both men and women were analysed separately. Data of study groups including only premenopausal women, only postmenopausal women, and pre- and postmenopausal women were combined to form an overall female group.

Sensitivity analysis

A sensitivity analysis was performed excluding studies that might be sources of uncertainty in order to test the validity of the meta-analysis. Studies with a high risk of bias according to the criteria mentioned above were excluded. High-quality studies were still excluded if iron supplements were used or the results as arithmetic mean were calculated from effect measures using median or geometric mean.

Results

Description of studies

Results of the search

Data of eligible publications were retrieved until July 12th, 2016. The literature search resulted in 324 published articles. After restriction to studies in English and German published in 1972 or later 310 articles remained, with 70, 112, 121, and 7 studies found on Pubmed, Scopus, Embase, and CENTRAL, respectively. The exclusion of duplicates led to 140 articles of which the abstract was screened for eligibility. Full-text articles were

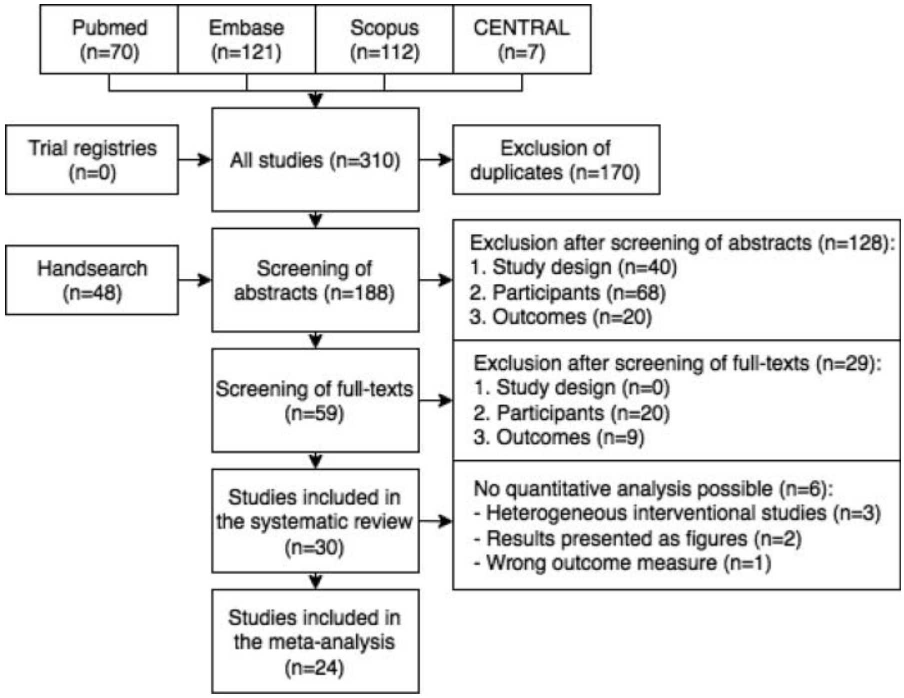

Figure 1. Flow-chart showing the study selection process.

retrieved for 45 studies and after screening 24 were deemed eligible for the systematic review and meta-analysis. No relevant studies were found when searching the trial registries described in section 3.1. The process is presented in Figure 1.

Included studies

Three interventional studies were eligible to be included in the systematic review, two of which were RCTs. Characteristics are presented in Table 2. One of the studies was published as two separate papers, which were treated like a single publication after the screening of abstracts (Wirths et al., 1987; Wirths et al., 1988).

Furthermore, 27 relevant studies were identified examining the iron status of vegetarians and matched omnivores in a cross-sectional way. 24 of these are cross-sectional studies, while the remaining three are interventional studies, which evaluated Fer in a vegetarian and matched omnivorous sample before starting the intervention (Brune et al., 1989; Fairweather-Tait et al., 1988; Schlesier et al., 2012). Therefore, the data were treated as those of cross-sectional studies. Characteristics of all these studies are presented in Table 3.

No cohort studies or case-control studies relevant to the research question were found.

Only one of the studies included was published in German, while all other studies were published in English.

Most of the studies included, i.e., one third, were published in the years 1990 to 1999, whereas no relevant study was published earlier than 1980. Recent studies published from 2010 up to the time of the literature search constitute nearly one quarter of all studies included in the systematic review, as well as studies published between 1980 and 1989. One fifth of included studies were published between 2000 and 2009.

Table 2. Characteristics of the included interventional studies.

	Participants				
	Women		Men		
First Author	n	Age (y)*	n	Age (y)	Design
Hunt and Roughead (1999)	21	20–42, 33.2 ± 7.0	/	/	The participants were randomly assigned to follow a LOV or NV diet planned by registered dietitians for 8 weeks, after which they switched to the other diet for another 8 weeks. Blood was analysed after 7 and 8 weeks of each diet and the average of both values estimated.
Wells et al. (2003)	/	/	21	59–78	All participants followed a self-selected LOV diet supplemented with texturised vegetable protein meat-analog products (TVP) for 2 weeks. Afterwards they were randomly allocated to further receive TVP or switch to beef products for another 12 weeks while participating in resistive training (RT) 3 times per week. Blood was analysed in week 2 of the baseline period and weeks 5 and 12 of RT.
Wirths et al. (1987), Wirths et al. (1988)	30	52.6 ± 14.3	3	47.7 ± 12.7	Participants followed a mixed diet for three weeks and afterwards switched to a LOV diet. Blood was analysed at the beginning and end of each period.

Age of participants is given as minimum-maximum and/or mean ± SD, if not otherwise specified.

Table 3. Characteristics of the included cross-sectional studies.

	Women				Men				Type of vegetarian diet	
	Vegetarians		Omnivores		Vegetarians		Omnivores			
Study	n	Age (y)*	n	Age (y)	n	Age (y)	n	Age (y)	Original definition	Adapted
Alexander et al. (1994)	VEG 31 V 5	Mean 26	36	age matched	14	Mean 28	14	age matched	VEG: No RM; F or P $\leq$1/wk V: No M, D, or E No distinction between groups	SV
Ball and Bartlett (1999)	LOV 48 V 2	18–45, 25.3 ± 6.4	24	18–45, 25.2 ± 6.2	/	/	/	/	LOV: RM $\leq$1/mth, F or P $\leq$1/wk V: No description No distinction between groups	SV
Bhatti et al. (2007)	J 22 B 36	18–55, J 32.3 ± 10.7, B 32.9 ± 11.3	50	18–55, 34.1 ± 11.3	J 100 B 100	18–55, J 33.8 ± 8.6, B 32.9 ± 11.3	100	18–55, 33.6 ± 11.2	J: "Strict Jain diet" B: "Strictly vegetarian"	VEG
Brune et al. (1989)	9	35–74, 60.3 ± 12.3	3	24–63, 49.3 ± 22.0	4	47–76, 63.8 ± 12.1	3	45–69, 53.7 ± 13.3	LV: No M, F, or E V: Additionally no D No distinction between groups	LV
Deriemaeker et al. (2010)	10	18–25, 19.8 ± 1.4	10	18–25, 20.5 ± 1.4	14	18–25, 20.6 ± 2.1	14	18–25, 20.9 ± 2.7	VEG: No RM, P, or F	LOV
Deriemaeker et al. (2011)	22	84.1 ± 5.1	23	84.3 ± 5.0	7	80.5 ± 7.5	7	80.6 ± 7.3	LOV: No description	VEG
Faber et al. (1986)	19	18–40, mean 29	12	18–40, mean 27	14	18–40, mean 29	10	18–40, mean 27	VEG: No RM, P, or F	LOV
Fairweather-Tait et al. (1988)	7	mean 25.1	14	mean 31.8	5	mean 33.4	14	mean 35.1	VEG: No description	VEG
Haddad et al. (1999)	15	20–60, 36.0 ± 8.1	10	20–60, 33.5 ± 8.2	10	20–60, 36.0 ± 8.1	10	20–60, 33.5 ± 8.2	V: No RM, F, P, D, or E	V
Harman and Parnell (1998)	12	20–65, mean 43	12	20–65, mean 39	12	20–65, mean 49	11	20–65, mean 40	LV: No RM, P, F, E V: No animal-derived foods No distinction between groups	LV
Harvey et al. (2005)	29	18–45, 31 ± 6	RM 28 PF 29	18–45, RM 34 ± 6, PF 32 ± 7	/	/	/	/	LOV: No M or F	LOV
Hawk et al. (2012)	19	18–22, 19.68 ± 1.57	20	18–22, 20.65 ± 1.04	/	/	/	/	VEG: No M or F OV/V: No description No distinction between groups	LOV
Helman and Darnton-Hill (1987)	60	Mean 29.3	40	Mean 31	60	Mean 29.3	13	Mean 31	VEG: No RM, P, or F	LOV
Hua et al. (2001)	20	Mean 41	20	Mean 40	10	Mean 41	10	Mean 40	LOV: No M	LOV
Huang et al. (1999)	20	18–40, 25.5 ± 6.1	19	18–40, 21.7 ± 1.1	15	18–40, 23.6 ± 4.9	13	18–40, 22.7 ± 2.0	LOV: No M or F	LOV
Kajanachumpol et al. (2011)	60	30–50, 41.2 ± 6.4	45	30–50, 37.7 ± 5.9	49	30–50, 41.0 ± 6.6	41	30–50, 39.8 ± 5.6	V: No M. D or E <5/y	LOV
Kim and Bae (2012)	59	47–85, 63.03 ± 9.34	48	47–85, 62.13 ± 8.28	/	/	/	/	VEG: No description	VEG
Leonard et al. (2014)	23	18–35	48	18–35	/	/	/	/	VEG: No description "Partial vegetarians": No description No distinction between groups	SV
Li et al. (2000)	/	/	/	/	LOV 43 V 18	LOV 22–54, 34.9 ± 9.0 V 22–50, 33.0 ± 7.7	HM 18 MM 60	HM 21–50, 34.2 ± 9.4 MM 21–55, 38.3 ± 7.3	LOV: M <6/y V: No M or E, D <6/y HM: M $\geq$285g/d MM: M <285g/d	SV, LV
Locong (1986)	22	26.2 ± 4.6	18	22.0 ± 4.0	14	27.5 ± 4.5	14	21.2 ± 1.8	VEG: RM, P, or F $\leq$1/mth	SV
Outila et al. (1998)	11	35 ± 8	14	32 ± 7	/	/	/	/	LV: Daily consumption of D V: D provided less than 1/3 of the yearly calcium intake 6 participants consumed M 1–3 times during the study!	SV

Reddy and Sanders (1990)	I 23 C 18	25–40, I 34.5 ± 3.9, C 29.6 ± 3.9	22	25–40, 33.8 ± 3.7	/	/	/	/	VEG: No description	VEG
Schlesier et al. (2012)	10	19–32	15	19–32	4	19–32	5	19–32	LOV: No description	VEG
Shaw et al. (1995)	32	20–30, 24.8 ± 4.0	39	20–30, 20.3 ± 1.1	23	20–30, 22.6 ± 4.4	20	20–30, 20.6 ± 1.0	VEG: “Buddhist vegetarians completely exclude fleshy foods”	LOV
Wilson and Ball (1999)	/	/	/	/	LOV 39 V 10	20–50, LOV 33.3 ± 8.2 V 31.0 ± 5.6	25	20–50, 32.7 ± 8.8	LOV: No RM; P or F ≤1/wk V: No M, D, or E	SV, V
Worthington-Roberts et al. (1988)	20	28.9 ± 7.2	RM 16 PF 15	RM 31.0 ± 5.2 PF 27.9 ± 4.6	/	/	/	/	VEG: No RM; P or F ≤1/wk	SV
Yen et al. (2008)	17	34.8 ± 4.5	19	35.9 ± 4.1	4	34.8 ± 4.5	9	35.9 ± 4.1	VEG: No M or F	LOV

*Age of participants is given as minimum-maximum and/or mean ± SD, if not otherwise specified.
M = Meat, RM = Red meat, P = Poultry, F = Fish, D = Dairy products, E = Egg products, HM = High-meat group, MM = Moderate-meat group, J = Jain, B = Brahmin, I = Indians, C = Caucasians.

The studies were conducted in almost equal parts in Australia/New Zealand, Asia, Europe, and USA/Canada, whereas only one relevant publication conducted in Africa was identified and none was carried out by a South American study group.

Excluded studies

29 studies were excluded after screening the full-text publication. The most common reasons were a non-vegetarian diet consumed by the intervention/exposure group (Berglund et al., 1994; Davis et al., 1992; Doyle et al., 1999; Houston et al., 1997; Kim et al., 2007; Sarri et al., 2005; Snyder et al., 1989; Tetens et al., 2007) and some of the participants being younger than 18 years (Donovan and Gibson, 1995; Fordy and Benton, 1994; Leggett et al., 1990; Linpisarn et al., 1984; McEndree et al., 1983; Rangan, 1997; Schwarz et al., 2014), leading to the exclusion of eight and seven studies, respectively. Four studies investigated the iron status in vegetarians and non-vegetarians without measuring Fer (Armstrong et al., 1974; Gear et al., 1980; Latta and Liebman, 1984; Woo et al., 1998). Three studies did not present the results according to diet group (Heath et al., 2001; Mahida et al., 2008; Yajnik et al., 2006) and another three studies did not list the results for relevant outcomes at all (Chen et al., 1998; Gupta et al., 2004; Rauma et al., 1995). Two studies investigated vegetarian groups without omnivorous controls (Löwik et al., 1990; Obeid et al., 2002), one study used a wrong unit for Fer (Lee and Krawinkel, 2011), and one study excluded anaemic participants from the control group (Pongstaporn and Bunyaratavej, 1999). Exact reasons for exclusion of each study are listed in Table S2.

Risk of bias in included studies

Interventional studies

Table S3 lists the risk of bias for both included RCTs and Table S4 for the only included non-randomised controlled trial. The RCTs conducted by Hunt 1999 and Wells 2003 were evaluated using the Risk of Bias Assessment Tool provided by the Cochrane Collaboration (Higgins and Green, 2011. Available from www.cochrane-handbook.org). According to this tool, both studies show a high risk of bias as a lot of details on the study protocol are not reported in the publications. The remaining study by Wirths 1987/1988 was evaluated using the MINORS (Slim et al., 2003). Overall risk of bias was moderate to high with a score of eleven of 24 possible points. Points were deducted for missing details on methods for statistical analysis, recruitment of participants, blinding of outcomes, as well as the issue of using participants as their own controls with parameters being estimated at two different points in time.

Cross-sectional studies

Table S5 lists the risk of bias for all included cross-sectional studies. Only one of the studies had low risk of bias in all categories (Harvey et al., 2005). Another twelve studies qualified for inclusion during the sensitivity analysis due to a score of ≥5 points (Ball and Bartlett, 1999; Haddad et al., 1999; Hawk et al., 2012; Helman and Darnton-Hill, 1987; Huang et al., 1999; Kim and Bae, 2012; Li et al., 2000; Outila et al., 1998; Schlesier et al., 2012; Shaw et al., 1995; Wilson and Ball, 1999; Worthington-Roberts et al., 1988), while one study showed an overall high risk of bias in the female groups but low risk of bias for male groups, which were therefore eligible for inclusion in the sensitivity analysis (Kajanachumpol et al., 2011).

Two of these studies were still excluded during the sensitivity analysis due to inclusion of iron supplement users (Ball and Bartlett, 1999; Wilson and Ball, 1999), another two studies were only analysed qualitatively as they did not provide sufficient data for inclusion in the meta-analysis (Outila et al., 1998; Worthington-Roberts et al., 1988), and furthermore two studies were excluded due to self-calculation of results from median values (Harvey et al., 2005; Shaw et al., 1995).

Of the low-risk studies definitely being included during the sensitivity analysis, one did not differentiate between men and women (Helman and Darnton-Hill, 1987), while another probably included pre- and postmenopausal women (Haddad et al., 1999). Sensitivity analysis was therefore not possible for these gender subgroups, but results were still used for combining all female groups and/or all gender groups. Another three low-risk studies investigated SV (Kajanachumpol et al., 2011) or VEG (Kim and Bae, 2012; Schlesier et al., 2012). This has to be kept in mind during the interpretation of results.

Main results

Systematic Review

None of the interventional studies investigating the effect of a meatless diet on iron stores in premenopausal women, pre- and postmenopausal women, and/or men found a significant change in Fer after following a LOV diet for 21 days, eight weeks, or twelve weeks (Hunt and Roughead, 1999; Wells et al., 2003; Wirths et al., 1987; Wirths et al., 1988).

The results of the cross-sectional studies are shown in Tables 4 and 5. Half of those investigating women, i.e. eleven of 22 studies, found no significant difference between diet groups (Brune et al., 1989; Deriemaeker et al., 2011; Deriemaeker et al., 2010; Faber et al., 1986; Fairweather-Tait et al., 1988; Haddad et al., 1999; Harman and Parnell, 1998; Harvey et al., 2005; Hawk et al., 2012; Locong, 1986; Schlesier et al., 2012), while ten studies reported significantly higher Fer values in the NV diet group (Alexander et al., 1994; Ball and Bartlett, 1999; Huang et al., 1999; Kajanachumpol et al., 2011; Kim and Bae, 2012; Leonard et al., 2014; Outila et al., 1998; Reddy and Sanders, 1990; Wilson and Ball, 1999; Worthington-Roberts et al., 1988) and one study found Fer to be significantly lower in Jain VEG compared to Brahmin VEG and Muslim NV, which did not differ significantly from each other (Bhatti et al., 2007).

Eight of 16 studies investigating males reported significantly higher Fer values in the NV population (Alexander et al., 1994; Deriemaeker et al., 2010; Faber et al., 1986; Haddad et al., 1999; Kajanachumpol et al., 2011; Li et al., 2000; Shaw et al., 1995; Wilson and Ball, 1999), while six studies found no significant difference (Brune et al., 1989; Deriemaeker et al., 2011; Fairweather-Tait et al., 1988; Harman and Parnell, 1998; Huang et al., 1999; Locong, 1986), and one study reported Brahmin VEG to not differ significantly from Muslim NV while Jain VEG and combined Brahmin and Jain groups had significantly lower Fer values (Bhatti et al., 2007). Interestingly, one study found results for VEG to be significantly higher than for NV,

Table 4. Results of the included cross-sectional studies investigating male or female groups for Fer [μg/L].

Study	Effect measure	Women			Men		
		Vegetarians	Omnivores	Level of significance	Vegetarians	Omnivores	Level of significance
Alexander (1994)	$\bar{x} \pm$ SD	13.6 ± 7.5	33.6 ± 54.3	$p < 0.01$	36.6 ± 36.0	105.4 ± 78.7	$p < 0.01$
Ball (1999)	$\bar{x} \pm$ SD	25 ± 16.2	45.5 ± 42.5	$p < 0.025$			
Bhatti (2007)	$\bar{x} \pm$ SD	B: 58 ± 22 J: 38.9 ± 15.6 B+J: 50.8 ± 21.8	51.5 ± 23.9	NS $p < 0.05$ NS	B: 78.9 ± 59.5 J: 58.5 ± 42.8 B+J: 68.7 ± 52.7	92.5 ± 72.9	NS $p < 0.0001$ $p = 0.0014$
Brune (1989)	$\bar{x} \pm$ SD	38.2 ± 12.2	62 ± 48.5	NS	84.5 ± 76.6	109.3 ± 133.1	NS
Deriemaeker (2010)	$\bar{x} \pm$ SD	22 ± 12	51 ± 15	NS	50 ± 19	73 ± 29	$p < 0.05$
Deriemaeker (2011)	$\bar{x} \pm$ SD	70 ± 46	158 ± 180	NS	47 ± 26	161 ± 165	NS
Faber (1986)	$\bar{x} \pm$ SD	16.1 ± 12.9	47.3 ± 35.7	NS	60.7 ± 103.9	146.8 ± 82.5	$p < 0.05$
Fairweather-Tait (1988)	Geometric mean ± pooled geometric SEM	9.6 ± 1.04	16.6 ± 1.04	NS	44.2 ± 1.04	45.3 ± 1.04	NS
Haddad (1999)	$\bar{x} \pm$ SD	27 ± 16	22 ± 13	NS	72 ± 32	141 ± 93	$p < 0.05$
Harman (1998)	$\bar{x} \pm$ SD	50.4 ± 35.3	59.6 ± 46.2	NS	79.8 ± 30.3	148.0 ± 161.7	NS
Harvey (2005)	Median (IQR) $\bar{x} \pm$ SD	11.1 (6.4–20.4) 12.6 ± 10.5	RM 6.8 (3.3–16.3) PF 17.5 (11.3–22.4) RM 8.8 ± 9.8 PF 17.1 ± 8.4 RM+PF 13.0 ± 9.9	NS NS NS NS NS	/	/	
Hawk (2012)	$\bar{x} \pm$ SD	23.16 ± 15.54	27.75 ± 18.01	NS	/	/	
Huang (1999)	$\bar{x} \pm$ SD	17.9 ± 10.3	40.0 ± 20.9	$p \leq 0.05$	46.2 ± 18.1	69.9 ± 22.6	NS
Kajanachumpol (2011)	Median (R) $\bar{x} \pm$ SD	19 (4–638) 34.7 ± 81.78	28 (6–182) 39.87 ± 33.88	$p < 0.001$ NS	44 (7–173) 54.11 ± 41.39	132 (26–567) 159.15 ± 113.92	$p < 0.001$ $p < 0.0001$
Kim (2012)	$\bar{x} \pm$ SD	33.08 ± 25.09	44.33 ± 26.90	$p < 0.01$			
Leonard (2014)	$\bar{x} \pm$ SD	26.3 ± 18.7	42.3 ± 25.6	$p < 0.01$			
Li (2000)	$\bar{x} \pm$ SD	/	/		SV 48 ± 29 OV 50 ± 29 OV+SV 48.6 ± 28.8	HM 153 ± 117 MM 111 ± 86 HM+MM 120.7 ± 94.9	$p < 0.05$ HM vs. MM $p < 0.01$ OV vs. MM $p < 0.001$ SV vs. HM, SV vs. MM, OV vs. HM $p < 0.0001$ OV + SV vs. HM + MM Otherwise NS
Locong (1986)	$\bar{x} \pm$ SD	33 ± 9	45 ± 28	NS	88 ± 42	107 ± 60	NS
Outila (1998)	Results are presented in Figure 2, making it impossible to abstract data for quantitative analysis.			$p = 0.009$	/	/	
Reddy (1990)	Geometric mean (95% CL) $\bar{x} \pm$ SD	C 11.1 (6.7–18.4) C, no supplements 10.4 (5.8–18.4) I 7.9 (4.8–12.9) I, no supplements 6.4 (3.8–11.8) C, no supplements 13 ± 9.9 I, no supplements 8.8 ± 7.4 C+I, no supplements 10.7 ± 8.7	C 20 (15.9–25.1) C, no supplements 18 (11.2–29.2) C, no supplements 22.7 ± 17.2	Significant	/	/	
Schlesier (2012)	$\bar{x} \pm$ (R) $\bar{x} \pm$ SD	21.6 (4.1–80.4) 31.86 ± 44.74	25.3 (3.1–76) 31.71 ± 22.22	NS	53.3 (10.3–99.2) 67.7 ± 40.47	37.5 (13.9–64.8) 42.3 ± 31.19	$p < 0.05$ NS
Shaw (1995)	Median (R) $\bar{x} \pm$ SD	12 (3–74) 25.66 ± 17.15	27 (3–145) 51.1 ± 33.02	$p \leq 0.05$	47 (9–182) 72.3 ± 44.84	91 (37–532) 192.59 ± 132.53	$p \leq 0.05$
Wilson (1999)	$\bar{x} \pm$ SD	/	/		V 65 ± 50 SV 64 ± 47 V + SV 64.2 ± 47.1	121 ± 73	$p < 0.05$ $p < 0.001$ $p = 0.0001$
Worthington-Roberts (1988)	Results are presented in Figure 3, making it impossible to abstract data for quantitative analysis.			$p = 0.01$	/	/	

NS = Non-significant, RM = Red meat group, PF = Poultry and fish group, HM = High-meat group, MM = Moderate-meat group, J = Jain, B = Brahmin, I = Indians, C = Caucasians.

which may be due to the very low number of participants (Schlesier et al., 2012).

All three studies investigating combined groups of men and women found significantly lower Fer in the vegetarian diet groups (Helman and Darnton-Hill, 1987; Hua et al., 2001; Yen et al., 2008).

19 studies provided information on the number of participants below cut-off values for Fer (Table S6). In premenopausal women

Table 5. Results of the included cross-sectional studies investigating combined male and female groups for Fer [μg/L].

Study	Effect measure	Vegetarians	Omnivores	Level of significance
Helman 1987	$\bar{x} \pm$ SD	45 ± 33	70 ± 61	$p < 0.05$
Hua 2001	$\bar{x}$(95%CI)	35 (21, 49)	72 (45, 100)	$p = 0.0012$
	$\bar{x} \pm$ SD	35 ± 37.49	72 ± 73.65	
Yen 2008	$\bar{x} \pm$ SD	45.6 ± 69.8	103.5 ± 157.0	$p < 0.05$

for example similar percentages of participants below cut-off levels in both diet groups were found in three studies investigating LOV (Harvey et al., 2005; Hawk et al., 2012) and SV with some participants in both groups using iron supplements (Ball and Bartlett, 1999). Six studies found a higher number of LOV (Faber et al., 1986; Shaw et al., 1995), SV (Worthington-Roberts et al., 1988), SV including two participants taking iron supplements (Outila et al., 1998), and VEG (Reddy and Sanders, 1990; Schlesier et al., 2012) to be below cut-off levels than NV.

Results for studies providing information on the same cut-off values have been combined in Table 6. The difference between diet groups in premenopausal women and all women was most apparent when the cut-off was defined as being <20 μg/L, <15 μg/L, and <12 μg/L, while percentages of women with even lower Fer values of <10 μg/L did not differ considerably between diet groups. Percentages of women with a cut-off level of <25 μg/L were also similar. Male vegetarians had distinctly higher percentages of participants falling below cut-off levels, especially when imposing cut-off levels of < 25 μg/L and < 20 μg/L for Fer.

Meta-analysis

As the study designs of included interventional studies were very heterogeneous, no quantitative analysis was performed. 24 studies were included in the meta-analysis of cross-sectional studies, ten of which investigated LOV (Deriemaeker et al., 2010; Faber et al., 1986; Harvey et al., 2005; Hawk et al., 2012; Helman and Darnton-Hill, 1987; Hua et al., 2001; Huang et al., 1999; Kajanachumpol et al., 2011; Shaw et al., 1995; Yen et al., 2008), three LV (Brune et al., 1989; Harman and Parnell, 1998; Li et al., 2000), two V (Haddad et al., 1999; Wilson and Ball, 1999), five VEG (Bhatti et al., 2007; Deriemaeker et al., 2011; Kim and Bae, 2012; Reddy and Sanders, 1990; Schlesier et al., 2012), and four primarily SV (Alexander et al., 1994; Ball and Bartlett, 1999; Leonard et al., 2014; Locong, 1986), while two of the other studies additionally included SV groups (Li et al., 2000; Wilson and Ball, 1999). One cross-sectional study was not included in the meta-analysis as results were presented as geometric mean with pooled geometric SEM (Fairweather-Tait et al., 1988). Another two cross-sectional studies are only discussed qualitatively, as results are presented in the form of figures, making it impossible to abstract the data for a meta-analysis (Outila et al., 1998; Worthington-Roberts et al., 1988).

When comparing LOV + LV + OV + V with NV (Fig. 2) significantly lower Fer values were found for vegetarians in premenopausal women (−17.70 μg/L, 95% CI [−29.80, −5.60], $p < 0.01$), all female groups (−13.50 μg/L, 95% CI [−22.96, −4.04], $p < 0.01$) (not shown in the forest plot to avoid double counting of female participants), studies that combined male and female groups (−30.80 μg/L, 95% CI [−47.24, −14.35], $p < 0.01$), men (−61.88 μg/L, 95% CI [−85.59, −38.17], $p < 0.01$), and all studies combined (−29.71 μg/L, 95% CI [−39.69, −19.73], $p < 0.01$). None of the four studies on groups including pre- and postmenopausal women found a significant effect of diet on Fer values and the overall effect remained non-significant (1.13 μg/L, 95% CI [−8.48, 10.75], $p = 0.82$).

Heterogeneity was very low in combined pre- and postmenopausal groups, and combined male and female groups with $I^2 = 0\%$, but considerable in premenopausal women, combined female groups, men, and overall with $I^2 = 88\%$, $I^2 = 81\%$, $I^2 = 74\%$, and $I^2 = 84\%$, respectively.

Six studies as well as the female groups of Kajanachumpol (2011) were eliminated during the sensitivity analysis due to high risk of bias (Brune et al., 1989; Deriemaeker et al., 2010; Faber et al., 1986; Harman and Parnell, 1998; Hua et al., 2001; Kajanachumpol et al., 2011; Yen et al., 2008), one study due to iron supplement use (Wilson and Ball, 1999), and two studies due to self-calculation of results from median (Harvey et al., 2005; Shaw et al., 1995), resulting in a decreased significance in all comparisons. The effect remained significant in men (−64.88 μg/L, 95% CI [−104.80, −24.96], $p < 0.01$) and all groups combined (−2.56 μg/L, 95% CI [−50.65, −14.48], $p < 0.01$) but ceased to be significant in premenopausal women (−13.36 μg/L, 95% CI [−30.52, 3.80], $p = 0.13$) and all female groups (−7.36 μg/L, 95% CI [−22.87, 8.16], $p = 0.35$). No sensitivity analysis was possible for pre- and postmenopausal women and combined women and men, as only one study remained in each subgroup.

Heterogeneity increased slightly in combined female groups, men, and all groups combined, with $I^2 = 84\%$, $I^2 = 87\%$ and $I^2 = 89\%$, respectively, and slightly decreased in premenopausal women and all women with $I^2 = 81\%$.

Table 6. Percentages of vegetarians (VEG) and non-vegetarians (NV) below various cut-off levels according to gender.

	Premenopausal women					All women					Men				
		VEG		NV			VEG		NV			VEG		NV	
Cut-off [μg/L]	Studies	n	%	N	%	Studies	n	%	n	%	Studies	n	%	n	%
<25	2	29	55.2	35	48.6	4	52	42.3	48	50.0	4	67	19.4	41	7.3
<20	3	49	57.1	54	33.3	6	108	58.3	103	41.7	5	47	21.3	43	7.0
<15	2	21	52.4	29	17.2	5	102	15.7	92	10.9	4	218	1.4	116	0.9
<12	4	129	38.8	100	20.0	9	306	28.8	244	17.6	9	414	5.8	294	2.0
<10	4	79	26.6	114	25.4	7	109	22.9	141	22.7	4	33	2.0	29	0.0

n: total number of participants; %: percentage of *n* below cut-off.

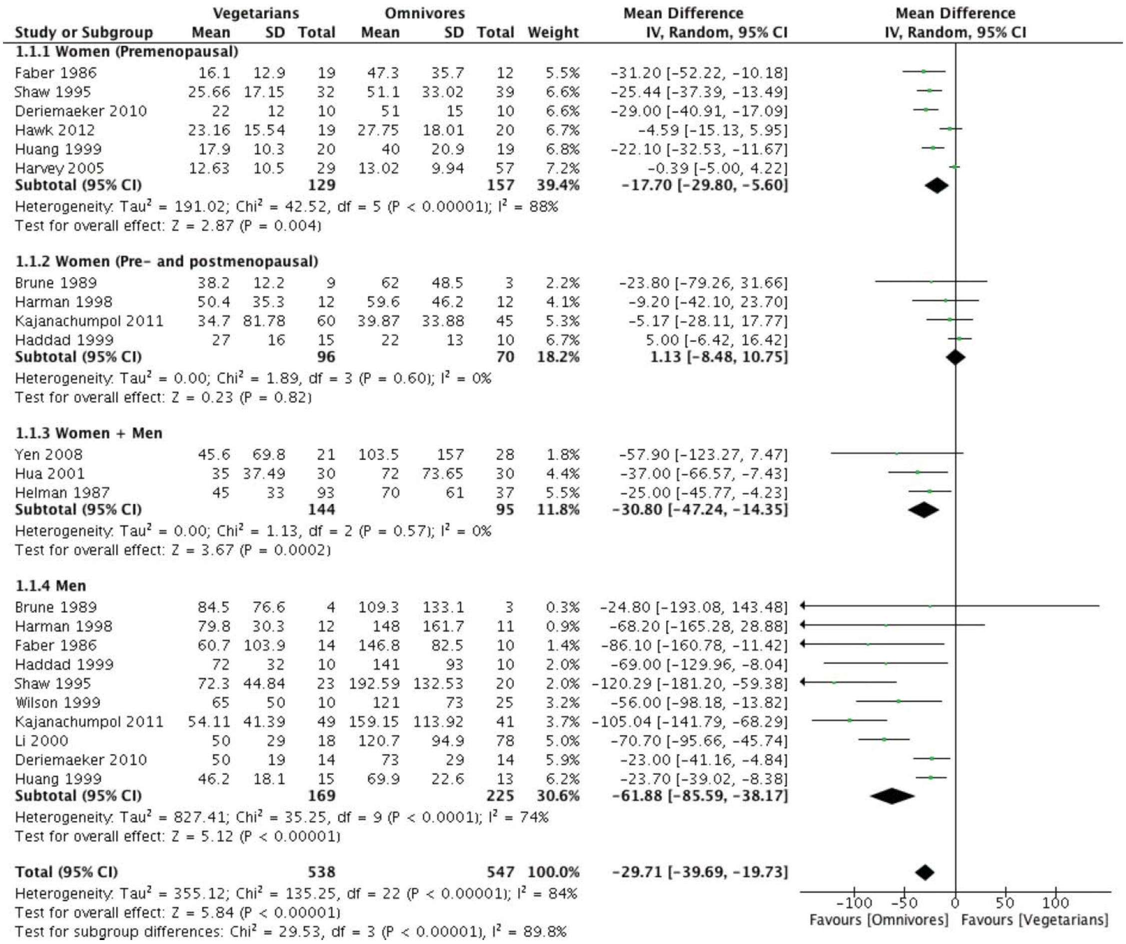

Figure 2. Forest plot showing pooled mean differences of serum ferritin (in μg/l) with corresponding 95% CI for the effects of LOV+LV+OV+V compared to non-vegetarians (omnivores). Study participants were separated in sub-groups according to gender as well as post- and premenopausal status. For each study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis. The diamond at the bottom of the graph represents the pooled MD with the 95% CI for all studies. Explanation of abbreviations, e.g. CI=confidence interval, I^2=heterogeneity.

The comparison of combined non- and low-meat-eaters with NV (Fig. 3) groups resulted in significantly lower Fer levels for LOV + LV + OV + V + VEG + SV in premenopausal women (-15.56 μg/L, 95% CI [-22.80, -8.33], $p < 0.01$), all women (-12.81 μg/L, 95% CI [-18.35, -7.27], $p < 0.01$) (not shown in the forest plot to avoid double counting of female participants), combined male and female groups (-30.80 μg/L, 95% CI [-47.24, -14.35], $p < 0.01$), men (-49.67 μg/L, 95% CI [-67.55, -31.78], $p < 0.01$), and all studies combined (-23.27 μg/L, 95% CI [-29.77, -16.76], $p < 0.01$). Combined pre- and postmenopausal female diet groups were not significantly different from each other (-3.19 μg/L, 95% CI [-10.79, 4.40], $p = 0.41$), as were postmenopausal female diet groups (-38.58 μg/L, 95% CI [-110.62, 33.45], $p = 0.29$).

Heterogeneity was very low in pre- and postmenopausal women and combined male and female groups with $I^2 = 20\%$ and $I^2 = 0\%$, respectively, but high in premenopausal women ($I^2 = 79\%$), postmenopausal women ($I^2 = 70\%$), all women ($I^2 = 71\%$), men ($I^2 = 73\%$), and all gender groups ($I^2 = 79\%$).

After excluding twelve studies and the female group of another study during the sensitivity analysis due to high risk of bias (Alexander et al., 1994; Bhatti et al., 2007; Brune et al., 1989; Deriemaeker et al., 2011; Deriemaeker et al., 2010; Faber et al., 1986; Harman and Parnell, 1998; Hua et al., 2001; Kajanachumpol et al., 2011; Leonard et al., 2014; Locong, 1986; Reddy and Sanders, 1990; Yen et al., 2008), two studies due to self-calculated results from median (Harvey et al., 2005; Shaw et al., 1995), and two more studies due to iron supplement use (Ball and Bartlett, 1999; Wilson and Ball, 1999), significance decreased in men (-49.36 μg/L, 95% CI [-87.69, -11.03], $p = 0.01$), and combined gender groups (-24.10 μg/L, 95% CI [-38.34, -9.85], $p < 0.01$). Differences between diet groups ceased to be significant for premenopausal women (-11.18 μg/L, 95% CI [-25.57, 3.21], $p = 0.13$) and all women (-7.72 μg/L, 95% CI [-17.68, 2.24], $p = 0.13$). A sensitivity analysis of pre- and postmenopausal women, postmenopausal women, and combined male and female groups was not possible, as only one study remained in each subgroup.

Heterogeneity decreased in premenopausal women ($I^2 = 67\%$) and combined female groups ($I^2 = 69\%$), and increased in men ($I^2 = 88\%$), and all gender groups ($I^2 = 87\%$).

Comparison of SV and NV (Fig. 4) showed significantly lower Fer values in the SV groups for premenopausal women (-15.71 μg/L, 95% CI [-23.22, -8.19], $p < 0.01$), men (-56.37 μg/L, 95% CI [-79.46, -33.28], $p < 0.01$), all women (-16.35 μg/L, 95% CI [-23.28, -9.42], $p < 0.01$), and combined male and female groups (-31.99 μg/L, 95% CI [-47.03, -16.96], $p < 0.01$). Heterogeneity was very low in

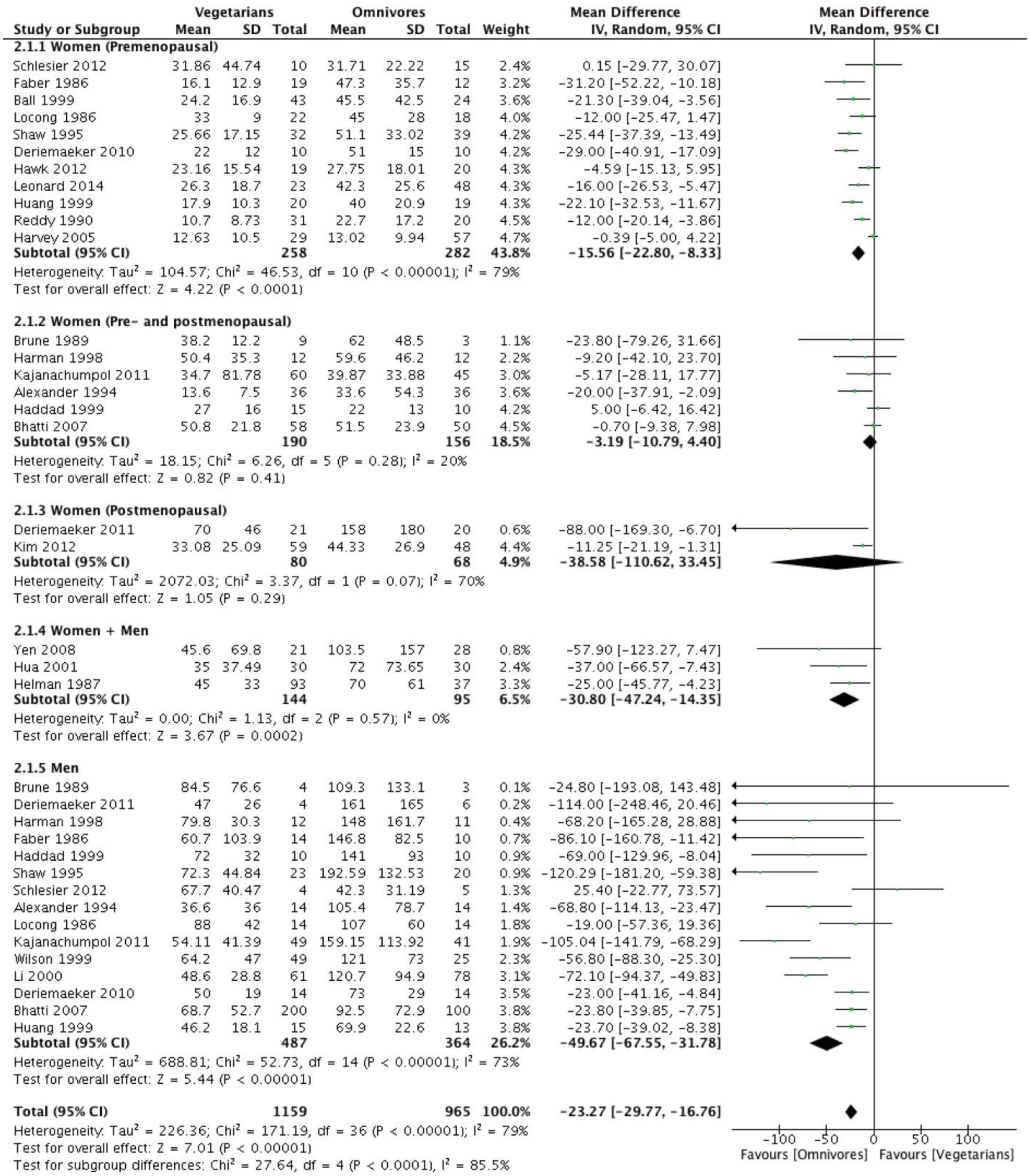

Figure 3. Forest plot showing pooled mean differences of serum ferritin (in μg/l) with corresponding 95% CI for the effects of LOV+LV+OV+V+VEG+SV compared to non-vegetarians (omnivores).

premenopausal women and all women with $I^2 = 0\%$, moderate in men with $I^2 = 48\%$, and high in combined gender groups with $I^2 = 77\%$ (Figure 4).

A sensitivity analysis was not possible, as only one study investigating male groups remained after exclusion of three studies due to high risk of bias (Alexander et al., 1994; Leonard et al., 2014; Locong, 1986) and two studies due to iron supplement use (Ball and Bartlett, 1999; Wilson and Ball, 1999).

Discussion

Our systematic review and meta-analysis showed that Fer levels are significantly lower for vegetarians, as well as low-meat eaters, compared to NV in all meta-analyses of cross-sectional studies according to gender with the exception of postmenopausal women and groups including pre- and postmenopausal women (Alexander et al., 1994; Bhatti et al., 2007; Brune et al., 1989; Deriemaeker et al., 2011; Haddad et al., 1999; Harman and Parnell, 1998; Kajanachumpol et al., 2011; Kim and Bae, 2012). However, significance decreased in all gender groups after excluding high-risk studies, studies including iron supplement users, and studies with self-calculated results during the sensitivity analysis, leading to a non-significant effect in premenopausal women and combined female groups, while results for men stayed significant.

The findings of this systematic review and meta-analysis are mostly in accordance with previous narrative reviews. It is widely acknowledged that vegetarians have lower iron stores than omnivores, as measured by Fer (Craig, 1994; Craig et al., 2009; Hunt, 2003; Lönnerdal, 2009; Saunders et al., 2013). This

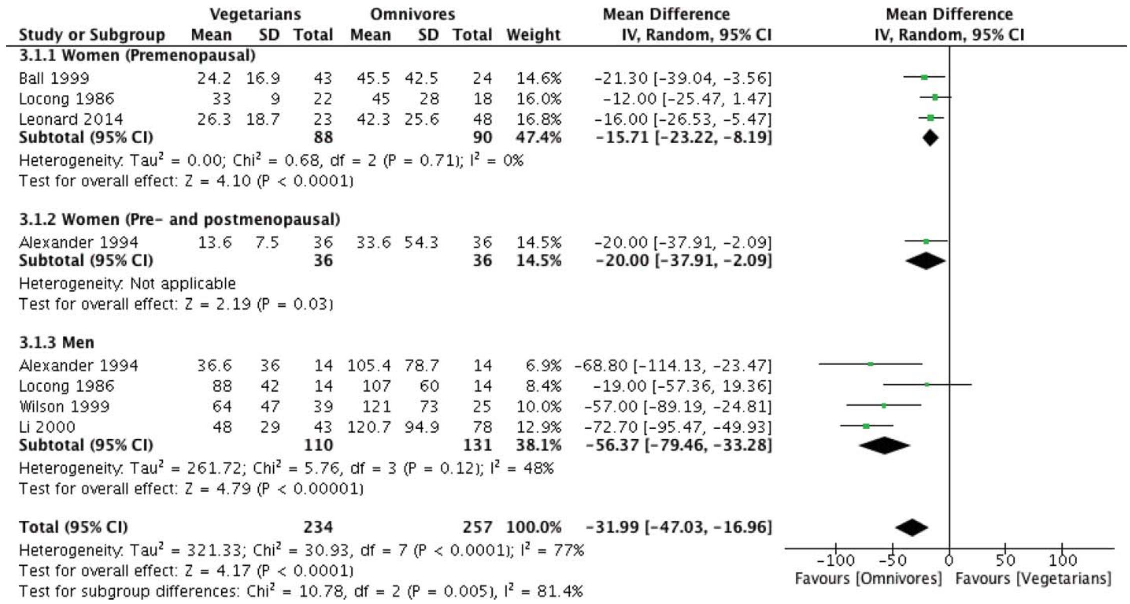

Figure 4. Forest plot for cross-sectional studies investigating Fer (in μg/l) in semi-vegetarians compared to non-vegetarians (omnivores).

was also apparent in this systematic review and meta-analysis. As no definite statement exists on whether ID without anaemia is more prevalent in vegetarians, studies providing information on participants below cut-off were synthesised and showed vegetarians of both genders to be at a higher risk for all cut-off values except very low Fer levels of <10 μg/L. This is in some discrepancy with previous reviews stating that Fer levels are lower in vegetarians than NV but not more likely to be below the normal range (Craig et al., 2009; Saunders et al., 2013). The reasons may be that previous reviews used a narrative approach and reported only on a few of the available studies, not taking into account the many small studies providing relevant data.

Interestingly, the differences in Fer levels between vegetarians and NV were more distinct in the male groups. This may be attributed to the fact that basic iron stores of NV males are in general higher than those of NV women, leading to a larger drop in iron stores after changing to a vegetarian diet. As the number of participants below cut-off levels was still much lower in all male groups compared to female groups, this effect does not lead to a higher risk for ID and IDA.

Several early studies in humans have shown that calcium exerts inhibitory effects on iron absorption (reviewed in (Lonnerdal, 2010)). In this regard iron absorption was inversely correlated to the calcium content of the meal in the range of physiological calcium intakes (Hallberg et al., 1991). Another study in 18 healthy volunteers showed a considerably lower iron bioavailability from cow's milk compared to human milk, which has an about 4 times lower calcium content than cow's milk (Hallberg et al., 1992). Therefore we also wanted to know whether there is a difference in the Fer levels between vegetarians consuming dairy products compared to those not eating milk and associated products. However, since there was no study available which has compared LOV or LV with V or OV it was not possible to extract the effect of milk or milk products on Fer levels. Nevertheless, comparing the results from the analyses of LOV + LV vs. NV with those from V vs. NV in men revealed no considerable difference between these two calculations (−62.74 [−90.77, −34.72] for LOV + LV vs. NV and −60.21 [−94.90, −25.52] for V vs. NV; data not shown in results). Therefore we can assume that dairy products do not have a high impact on Fer levels, although the study availability for this research question is restricted.

One major limitation of this review is that most of the studies had a cross-sectional design and thus a lower informative value than interventional studies. However, a potential problem of interventional studies is that the minimum duration of intervention to achieve significant effects on iron status and Fer values can vary and may not be easy to estimate. Another limitation of this review is that major iron intakes may vary widely between study populations and may lead to differences in iron status parameters between studies. However, most of the cross-sectional studies and all of the interventional studies included also provided information on the iron intake of participants. (Faber et al., 1986; Li et al., 2000; Shaw et al., 1995). Mean daily iron intake was reported to not differ significantly between diet groups in most of the studies, i.e., nine of 14 studies on males (Brune et al., 1989; Deriemaeker et al., 2011; Faber et al., 1986; Harman and Parnell, 1998; Huang et al., 1999; Locong, 1986; Shaw et al., 1995; Wells et al., 2003; Wirths et al., 1987; Wirths et al., 1988) and 14 of 20 studies on females (Ball and Bartlett, 1999; Brune et al., 1989; Deriemaeker et al., 2011; Deriemaeker et al., 2010; Faber et al., 1986; Haddad et al., 1999; Harman and Parnell, 1998; Hawk et al., 2012; Hunt and Roughead, 1999; Leonard et al., 2014; Locong, 1986; Reddy and Sanders, 1990; Wirths et al., 1987; Wirths et al., 1988; Worthington-Roberts et al., 1988). This contradicts evidence from large cohort studies stating that vegetarians have a higher total iron intake than NV (Cade et al., 2004; Clarys et al., 2014; Davey et al., 2003; Shridhar et al., 2014). A contributing factor may be the small sample size of included studies in this review, as differences have to be more distinct to be significant. Furthermore, evaluation of iron intake in the large studies was done via food-frequency questionnaire, while smaller studies used mostly food records for three to twelve days, which might be more representative of the actual dietary intake of participants.

As non-haem iron absorption is influenced by various food components, iron absorption rates are, in addition to total iron intake, also of special interest. However, none of the studies reported on the amount of absorbed iron, making it impossible to draw a conclusion on its effect on iron stores in this systematic review.

Another problematic issue of this systematic review and meta-analysis were the varying definitions of a vegetarian diet provided by studies as well as studies not defining the diet pattern of their vegetarian participants at all. Four studies for example had to be excluded during the screening of full-text publications due to a high or unclassified meat intake in the supposedly vegetarian study groups (Berglund et al., 1994; Kim et al., 2007; Sarri et al., 2005; Snyder et al., 1989).

Although vegetarian diets are associated with lower iron stores, which may increase the risk for iron deficiency anemia, it should also be mentioned that on the other hand high iron stores may also be detrimental to humans. Recent meta-analyses for example showed that high Fer levels were related to an increased risk of type 2 diabetes (Orban et al., 2014) and metabolic syndrome (Jin et al., 2015). The major discussed mechanism is (free) iron induced oxidative stress resulting in cellular damage (Hansen et al., 2014). So, in cases of high iron stores, especially in men, who have no additional iron losses through menstruation, a vegetarian diet may be an option to physiologically reduce the iron stores in order to gain health benefits. Furthermore several epidemiological studies have shown that vegetarian diets are associated with positive health outcomes, such as a reduced risk of incidence and/or mortality from ischemic heart disease and incidence of total cancer (reviewed in (Dinu et al., 2016)). A lower iron bioavailability and lower Fer levels may be involved in the protective effects of plant based diets in non-communicable diseases (Ekmekcioglu et al., 2016). Furthermore vegan diets have also been shown to improve glycaemic control and blood lipids (Trepanowski and Varady, 2015).

In conclusion our meta-analysis showed and confirmed several previous studies that adults eating vegetarian and vegan diets have lower iron stores compared to omnivores. This may have a special relevance during growth but also in conditions of high iron demands such as it is in pregnancy. Vegetarians with more or less depleted iron stores may also be prone to IDA especially in cases of chronic or acute blood losses, such as for example in gastrointestinal bleeding and severe injuries. On the other hand, lower iron stores may be protective against non-communicable diseases, such as type 2 diabetes (Orban et al., 2014). Therefore not only vegetarians but also non-vegetarians are advised to regularly control their iron status and improve their diet regarding the content and bioavailability of iron by consuming more plants and less meat.

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