Red Meat Intake and Risk of Rheumatoid Arthritis: A Categorical and Dose-Response Meta-Analysis

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Abstract

Objective: Findings from previous observational studies on the association between red meat intake and risk of rheumatoid arthritis (RA) are inconsistent. Therefore, we aimed to evaluate the impact of red meat intake on the incidence of RA by meta-analysis.

Methods: PubMed and Web of Science were searched for eligible observational studies regarding the association between red meat intake and the risk of RA until June 30, 2021. Risk estimates with corresponding 95% confidence interval (95% CI) were pooled. Subgroup analysis and meta-regression analysis were performed to explore the potential sources of heterogeneity. Sensitivity analysis and publication bias test were also carried out.

Results: A total of eleven studies were selected, involving 4 cohort studies with 5 203 identified cases from 349 776 individuals and 7 case-control studies with 3 762 cases and 6 856 controls. The pooled risk estimate of RA risk was 0.94 (95% CI: 0.77 to 1.15) for ever versus non/occasional red meat intake, while high dose of red meat intake increased the risk of RA (OR: 1.26, 95% CI: 1.07 to 1.50) in the categorical meta-analysis. Dose-response meta-analysis suggested a non-linear dose-response relationship between red meat intake and RA (P=0.028). Red meat intake was found to be a risk factor of RA when the dose ranged from 96 to 166 g/day.

Conclusion: High dose of red meat intake could increase the risk of RA. Mechanistic studies are warranted to clarify the aetiologic pathways through which high dose of red meat intake may promote RA.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that corrodes arthrosis and causes progressive articular damage [1]. The annual incidence rate of RA was 14.9% in 2017, which has increased 8.2% compared with that in 1990 around the world [2]. It was estimated that 20 to 30 percent of RA patients would be invalidity for work permanently without any medical treatment within two to three years of diagnosis [3].

Accumulating environmental risk factors have been found to play an important role in RA, such as smoking, breastfeeding, silica exposure and educational level [4–7]. Recently, it has received growing attention that dietary pattern and nutrients are potential modifiable factors affecting the occurrence and development of RA. For example, a population-based case-control study found that Mediterranean diet can protect against RA in the Swedish epidemiological investigation of RA [8]. Likewise, a large-scaled case-control study showed that consumption of oily fish was associated with a moderately reduced risk of RA [9]. In addition, a meta-analysis provided sufficient evidence that high intake of total vitamin D reduces the incidence of RA [10].

Red meat as a fundamental component of daily diet in humans, its association with RA has been gradually concerned, while the findings were controversial. In the cohort of Nurses' Health Study (NHS) and NHSII, Hu et al [11] found that lower red meat consumption had a protective effect on the risk of early-onset RA during 3,678,104 person-years. Also, another large cohort study consisting of 80,551 postmenopausal women in the United States came to the similar conclusion that red meat can promote the risk of RA [12]. However, several studies showed no statistically significant association between red meat intake and the incidence of RA [13–15]. Moreover, little is known regarding the dose-response relationship between the consumption of red meat and risk of RA.

Therefore, we performed a categorical and dose-response meta-analysis to clarify the relationship between red meat intake and risk of RA.

Methods

The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021267568). The PRISMA checklist for reporting the meta-analysis is shown in Supplementary Table 1.

Search strategy

PubMed and Web of Science were searched for observational studies investigating the association of red meat intake with risk of RA until June 30, 2021, without language restrictions. The subject terms were established as follow: ("meat" or "beef" or "veal" or "pork" or "lamb" or "mutton" or "horse" or "goat" or "bacon" or "ham" or "sausage" or "salami" or "hot dogs") and ("rheumatoid arthritis" or "RA"). In addition, references of related studies were also checked to identify additional publications of interest.

Inclusion and exclusion criteria

Studies meeting the following criteria were included: (1) study type was an observational study; (2) directly reported odds ratio (OR) or hazards ratio (HR) or relative risk (RR) with 95% confidence interval (CI) or indirectly provided relevant data for calculation; (3) if study populations overlapped, the one with larger sample size was included.

The exclusion criteria were as follows: (1) animal study, review, meta-analysis, letter or comment; (2) no access to full text; (3) with insufficient data to obtain risk estimates with 95% CI.

Two authors (Chen W and Liu K) independently evaluated the retrieved literature in full text, and discrepancies were resolved by a third author (Ye D).

Data extraction

Data was extracted cross-checked by two researchers (Chen W and Liu K) independently from eligible studies. The extracted information included name of first author, publication year, area, age, gender, type of study design, follow-up period, sample size, dose of red meat intake and the maximally adjusted OR, RR or HR with corresponding 95% CI.

Quality assessment

The Newcastle-Ottawa Scale (NOS) [16] was used to evaluate the quality of included studies with scores ranging from 0 to 9 points. Studies with a quality score of no less than 7 points were considered as high quality. Two reviewers (Sang X and Zhuang Y) assessed the quality, and discrepancies were resolved by consensus and discussion.

Statistical analysis

All analyses were performed within Stata version 13 (Stata Corp LP, College Station, TX). Cochran's Q test and I^2 statistics were utilized to assess the heterogeneity across the included studies [17]. Random-effects model was preferred when $p < 0.10$ and $I^2 > 50\%$; otherwise, fixed-effect model was applied.

In the categorical meta-analysis, ever red meat intake was compared with non/occasional red meat intake, which was defined by study-specific reference ranges. If the group of ever red meat intake was set up into multiple categories, we combined the effect estimates of different categories into a single value in each study. When the study reported mean and standard deviation (SD) of red meat intake between RA patients and controls rather than OR value, we transformed standardized mean difference (SMD) to OR according to the formula of ln OR= SMD [18]. If the study provided median and range of red meat intake, we computed mean and SD by the method of Hozo et al [19]. We also pooled the risk estimates comparing the highest with the lowest red meat intake among the studies with equal or more than three different categories of red meat intake. Moreover, subgroup analysis and meta-regression analysis were further performed based on food culture (western, oriental and Arab diet), publication year (<2018 and 2018), quality score (≥7 and <7), sample size (≥1000 and <1000). Furthermore, sensitivity analysis was used to check stability of the results by omitting one study at a time and combining the effect values of the remaining studies. Begg's test and Egger's test [20, 21] were used to evaluate publication bias.

For the dose-response meta-analysis, we used the method described by Greenland and Longnecker [22] to estimate the dose-response relationship between red meat intake and RA. If one study reported red meat intake by range, we assigned the midpoint of the lower and upper bound as mean or median was not provided. If the highest dose group was open-ended, the lower limit plus the width of the previous group was supposed as the corresponding consumption of red meat. When lowest dose group was open-ended, it was deemed zero as the lower bound of the reference group. If the consumption was shown by servings per day, we transformed it into grams per day using standard units of 120 g [23].

Results

Study selection

A total of 3 230 studies were searched and 11 eligible studies were finally included [8, 11-14, 24-29]. The details are shown in Figure 1. The basic characteristic of the literatures is presented in Table 1. Among 11 studies, there were 4 cohort studies [11-12,27,29] and 7 case-control studies [8,13-14,24-26,28]. In cohort studies, a total of 349 776 individuals participated, and 5 203 participants developed RA. In case-control studies involving 10 618 individuals included 3 762 RA cases and 6 856 controls. The studies were conducted in United States [11-13], United Kingdom [24], China [25], Japan [26], Sweden [8,27], Iran [14,28] and France [29]. Four studies [11-13, 29] recruited only women and the rest of them enrolled participators of both genders.

Categorical meta-analysis

Compared with non/occasional red meat intake, ever red meat intake was not significantly associated with risk of RA (OR: 0.94; 95% CI: 0.77 to 1.15; Figure 2A) with high heterogeneity (I^2=91.5%). Subgroup analysis showed that the association remained insignificant when stratified by food culture, publication year, quality score, sample size, study design and gender. However, the heterogeneity in the subgroup of western diet in food culture, publication year beyond 2018, quality score ≥7, sample size ≥1000, case-control in study type and female of gender all went down. The results of meta-regression analysis showed food culture might be a potential source of heterogeneity (*P*=0.023; table 2).

In the analysis of highest vs. lowest red meat intake, we excluded studies that only divided the red meat intake group into two groups [8, 16, 24, 26,]. Therefore, there were 7 studies included [11-13, 24, 27-29]. The forest plot showed that high red meat intake was associated with an increased risk of RA (OR: 1.26; 95% CI: 1.07 to 1.50; Figure 2B). In subgroup analysis, the positive associations were found among the studies with western diet culture, published before 2018, assessed with higher quality, performed by case-control study design or conducted in females. The associations were significant with larger (OR: 1.19; 95% CI: 1.02 to 1.38) or smaller (OR: 2.15; 95% CI: 1.29 to 3.59) sample size. However, some subgroups could provide no compelling information because the number of included studies was too few (Arab diet: N=1; Quality score <7: N=1). In addition, the heterogeneity was moderate (I^2= 56.7%) and the source of heterogeneity has not been found in meta-regression analysis (table 2).

Sensitivity analysis showed that no specific study affected the overall estimate. At the same time, there was no publication bias in the two parts of categorical meta-analysis (*P*= 0.876 and 0.230 of Begg's test respectively; *P*=0.766 and 0.119 of Egger's test respectively).

Dose-response relationship between red meat and RA

Four studies [11, 24, 27, 29] met the requirements for dose-response meta-analysis. A significant non-linear association between red meat intake and RA was found (*P*=0.028), as depicted in Figure 3. Increased risk of RA was observed when red meat intake ranging from 96 g/day to166 g/day. The most deleterious daily consumption of red meat was 148.5 g/day (OR: 1.27; 95% CI: 1.07 to 1.48) for risk of RA.

Discussion

Previous reviews [30–32] summarized the effect of red meat on risk of RA, while have not quantitively synthesized the evidence on the relationship between red meat intake and risk of RA. In the current study, we included a total of 11 observational studies for meta-analysis, and found no overall association between red meat consumption and risk of RA. Interestingly, we found that high red meat intake would promote the occurrence of RA, which suggested a threshold effect with an increased risk of RA only at high levels of red meat consumption. Moreover, a non-linear dose-response relationship was observed.

In the analysis of ever versus non/occasional red meat intake, the large heterogeneity deserved particular attention, which may be partly explained by different diet culture across the 11 studies. It is well known that dietary habits varied dramatically in the countries and regions with different diet culture. Western diet is mainly based on meat, milk, poultry, eggs and other animal food, thus always accompanied by high consumption of saturated fat and trans-fat [33]. Even though dichotomous meta-analysis found null association of red meat intake with risk of diet in countries with western diet culture, highest quintile of red meat intake had an

elevated risk of RA. On the other hand, studies conducted in countries and regions with oriental diet and Arab diet were relatively limited, more relevant studies should be supplemented for obtaining and confirming stable results.

Seven original studies evaluated the association comparing the highest with the lowest level for red meat intake with a moderate heterogeneity. A majority of included studies had high quality (85.7%) and large sample size (71.4%), which provides additional confidence in the findings from our pooled risk estimates. In addition, results from sensitivity analysis were stable and publication bias have not been detected. Furthermore, dose-response relationship meta-analysis suggested that there was statistically significant association between red meat intake and risk of RA when the dose of red meat intake reached a high level (96 ~ 166 g/day). Consistently, United Kingdom dietary guidelines endorse limiting the intake of both red and processed meat to 70 g/day [34]. The nonsignificant increased risk at red meat intake exceeding 166 g/day might result from relatively small sample size. Therefore, more epidemiological studies with large sample size are needed to clarify the dose-response relationship.

A positive association between high red meat intake and risk of RA is biological plausible [35–37]. One possible mechanism is that red meat intake affects the development of RA through iron cycle, since red meat is rich in iron, which is easy to accumulate in rheumatoid synovium and causes tissue damage [38–39]. Another explanation is the high collagen content in red meat. Pattison DJ [24] et al. demonstrated that individuals with high intake of red meat were at increased risk of RA because they are more likely to be sensitized to collagen and produce anti-collagen antibodies. Moreover, Stamp LK et al [40] suggested that abundant arachidonic acid (AA) in red meat raises the risk of RA. When AA is ingested in humans, it goes through a cascade reaction to produce eicosanoid with pro-inflammatory properties. The saturated fat in higher levels of red meat also can increase the risk of RA. Saturated fatty acids could translocate lipopolysaccharide toxin and release it into the bloodstream, thus stimulating the immune system and enhance inflammation [41].

There were some limitations should be noted. First, statistically significant heterogeneity among studies was observed. However, the use of random-effects model was allowed to take the heterogeneity among studies into account. Second, the definition of red meat may be not inclusive of all dietary sources of animal meat, nor they have been widely acknowledged across the different studies. Therefore, development and application of universally agreed definitions of red meat subtypes are unavoidable steps in future epidemiological studies aimed to investigate the association of red meat intake with risk of RA. Third, cutoff value of distinguishing between high and low consumption of red meat was diversiform in the included studies, which might introduce bias in an unpredictable direction of categorical meta-analysis. Finally, the imprecise measurement of red meat intake along with recall bias might affect the estimation of the association between red meat intake and risk of RA.

Conclusion

In conclusion, the meta-analysis showed that high red meat intake is associated with an increased risk of RA. However, high-quality prospective studies that employ standardized assessments of red meat intake and unified definitions of red meat levels are warranted, as well as the mechanistic studies to clarify the aetiologic pathways through which high red meat intake may lead to RA incidence.

Abbreviations

AA Arachidonic acid

CI Confidence interval

HR Hazards ratio

NHS Nurses' Health Study

NOS Newcastle-Ottawa Scale

OR Odds ratio

RA Rheumatoid arthritis

RR Relative risk

SD Standard deviation

SMD Standardized mean difference

Declarations

Ethics approval and consent to participate Not applicable.

Disclosure statement The authors have declared no conflicts of interest.

Consent for publication Not applicable.

Availability of data and materials All data generated or analyzed during this study are included in this published article.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions Ye D conceived and designed the study. Chen W and Liu K performed literature search. Sang X and Zhuang Y assessed the quality of included studies according NOS. Ye D resolved the argument between Chen W and Liu K. Chen W, Liu K, Su Q and Hu Y performed data analysis. Chen W drafted the manuscript and He Z, Huang L and Mao Y revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of included studies

Author, year	Country	Study type	Age/Sex	Research period	Cases/cohort size or controls	Quantity	Type of metric	Quality
Shapiro JA, 1996 [13]	USA	case-control	18-64/Female	1971-1975	324/1 245	4.4~6.5 servings/week vs. < 4.4 servings/week	OR	7
						6.5~9.1 servings/week vs. <4.4 servings/week		
						> 9.1 servings/week vs. <4.4 servings/week		
Pattison DJ, 2004 [24]	UK	case-control	45-75/Both	1993-1997	88/176	25.5-58.0 g/day vs. <25.5 g/day	OR	6
						> 58.0 g/day vs. <25.5 g/day		
He J, 2016 [25]	China	case-control	NA/Both	2012-2013	968/1 037	Mean (SD)	SMD to OR	4
Hu Y, 2017 [11]	USA	cohort	25-55/Female	1984-2011	1 007/170 996	Median: 0.72 servings/day vs. 0.37 servings/day	HR	7
						Median: 1.04 servings/day vs. 0.37 servings/day		
						Median: 1.50 servings/day vs. 0.37 servings/day		
Matsumoto Y, 2017 [26]	Japan	case-control	NA/Both	2010-2011	208/205	Mean (25th-75th percentiles)	SMD to OR	5
Johansson K,2018 [8]	Sweden	case-control	Median: 53/Both	2005-2014	1 721/3 667	Mean (SD)	SMD to OR	7
Krok-Schoen JL, 2018 [12]	USA	cohort	55-79/Female	1993-1998	3 348/80 551	0.303~0.562 servings/day vs. <0.303 servings/day	HR	7
						0.562~0.932 servings/day vs. <0.303 servings/day		
						0.932 servings/day vs. <0.303 servings/day		
Rambod M, 2018 [14]	Iran	case-control	>18/Both	2015-2016	403/426	Mean (SD)	SMD to OR	6
Sundström B, 2019 [27]	Sweden	cohort	54-89/Both	2003-2014	368/35 600	4~7 servings/week vs. ≤4 servings/week	HR	8
						7~10 servings/week vs. ≤4 servings/week		
						>10 servings/week vs. ≤4 servings/week		
Mosalmanzadeh N, 2020 [28]	Iran	case-control	19-68/Both	2017-2018	50/100	T2 vs. T1	OR	8
						T3 vs. T1		
Nguyen Y, 2020 [29]	France	cohort	40-65/Female	1990-2017	480/62 629	51~104 g/day vs. <51 g/day	HR	8
						>104 g/day vs. <51 g/day		

Abbreviation: HR: hazard ratio; NA: not available; OR: odds ratio; SD: standard deviation; SMD: standardized mean difference; T: tertiles.

Table 2 Subgroup analysis and meta-regression between red meat intake and risk of RA.

		Ever vs. Non/occasional red meat intake					Highest vs lowest red meat intake				
		No.	OR (95% CI)	P value	I^2% of heterogeneity test	Interlayer heterogeneity P value	No.	OR (95% CI)	P value	I^2% of heterogeneity test	Interlayer heterogeneity P value
Total		11	0.94 (0.77~1.15)	0.556	91.5		7	1.26 (1.07~1.50)	0.007	56.7	
Food culture											
	Western diet	7	1.06 (0.96~1.17)	0.240	51.3	0.023	6	1.21 (1.04~1.41)	0.013	49.0	0.159
	Oriental diet	2	0.36 (0.08~1.66)	0.190	98.2		/	/	/	/	
	Arab diet	2	1.43 (0.67~3.02)	0.353	84.7		1	2.40 (1.19~4.85)	0.015	56.7	
Publication year											
	2018 before	5	0.76 (0.41~1.40)	0.371	96.0	0.317	3	1.51 (1.17~1.95)	0.371	24.1	0.103
	2018 beyond	6	1.03 (0.94~1.12)	0.512	37.8		4	1.13 (0.97~1.33)	0.512	41.0	
Quality score											
	≥7	3	1.16 (0.89~1.51)	0.272	73.0	0.355	6	1.24 (1.05~1.47)	0.014	59.1	0.418
	<7	8	0.85 (0.65~1.11)	0.241	93.5		1	1.90 (0.90~4.01)	0.092	NA	
Sample size											
	≥1000	7	1.01 (0.90~1.13)	0.884	72.1	0.834	5	1.19 (1.02~1.38)	0.023	50.7	0.094
	<1000	4	0.84 (0.29~2.42)	0.741	96.6		2	2.15 (1.29~3.59)	0.003	0.0	
Study type											
	Cohort	4	1.10 (0.94~1.27)	0.230	69.0	0.523	4	1.19 (0.99~1.43)	0.063	42.3	0.297
	Case-control	7	0.85 (0.59~1.22)	0.376	93.9		3	1.60 (1.05~2.46)	0.031	42.3	
Sex											
	Female	4	1.08 (0.91~1.29)	0.396	71.3	0.609	4	1.22 (1.02~1.46)	0.034	62.2	0.503
	Both	7	0.87 (0.62~1.15)	0.402	94.1		3	1.57 (0.92~2.68)	0.098	60.6	

Figures

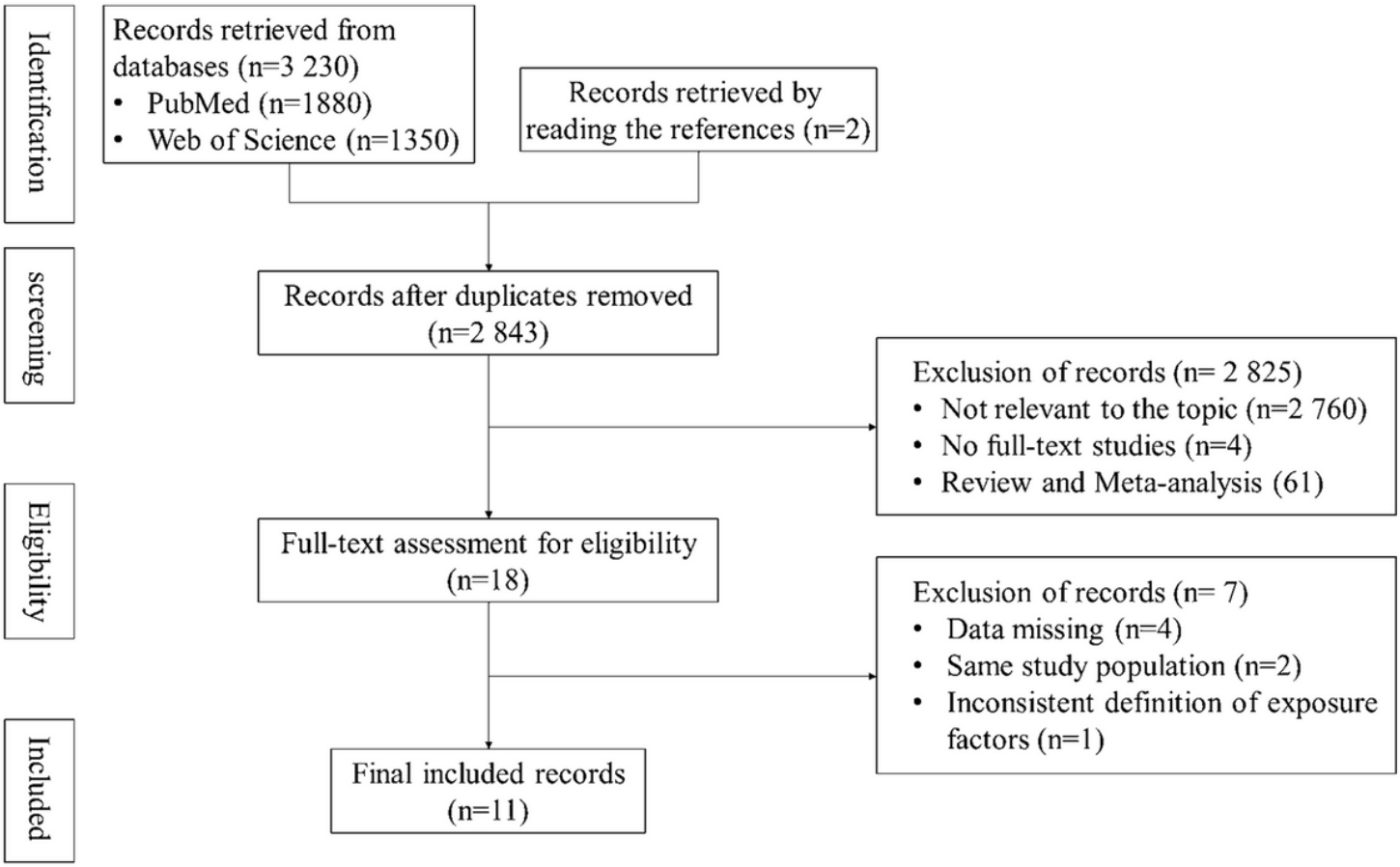

Figure 1

The flow diagram of study selection.

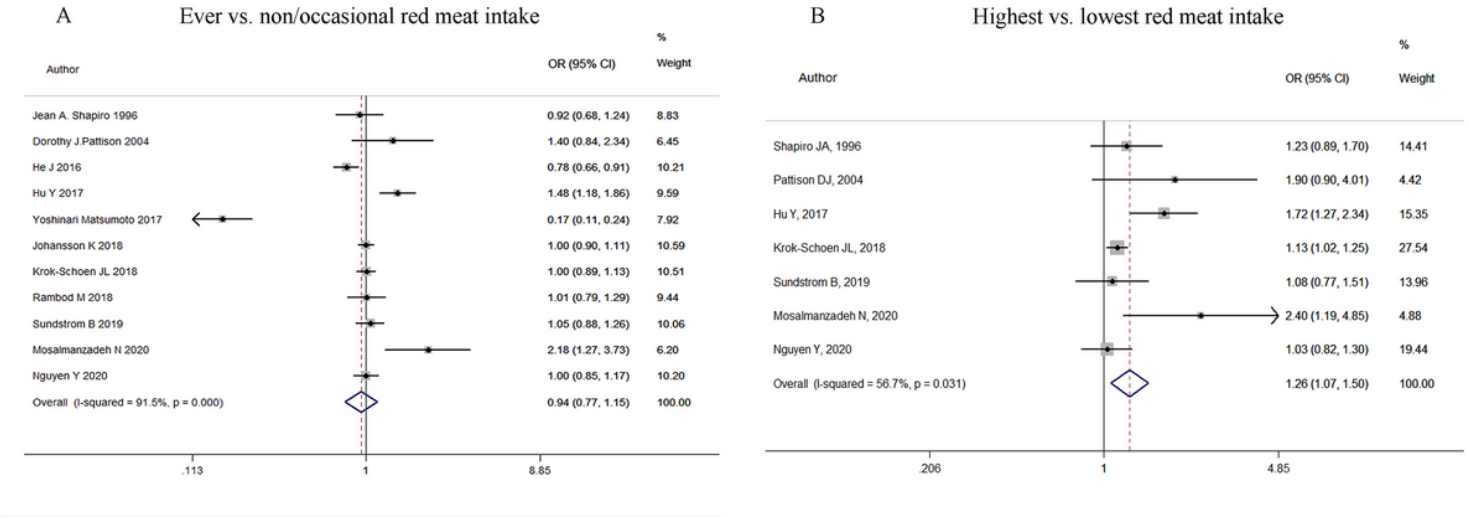

Figure 2

Association between red meat intake and risk of RA comparing ever vs. non/occasional (A) and highest vs. lowest (B).

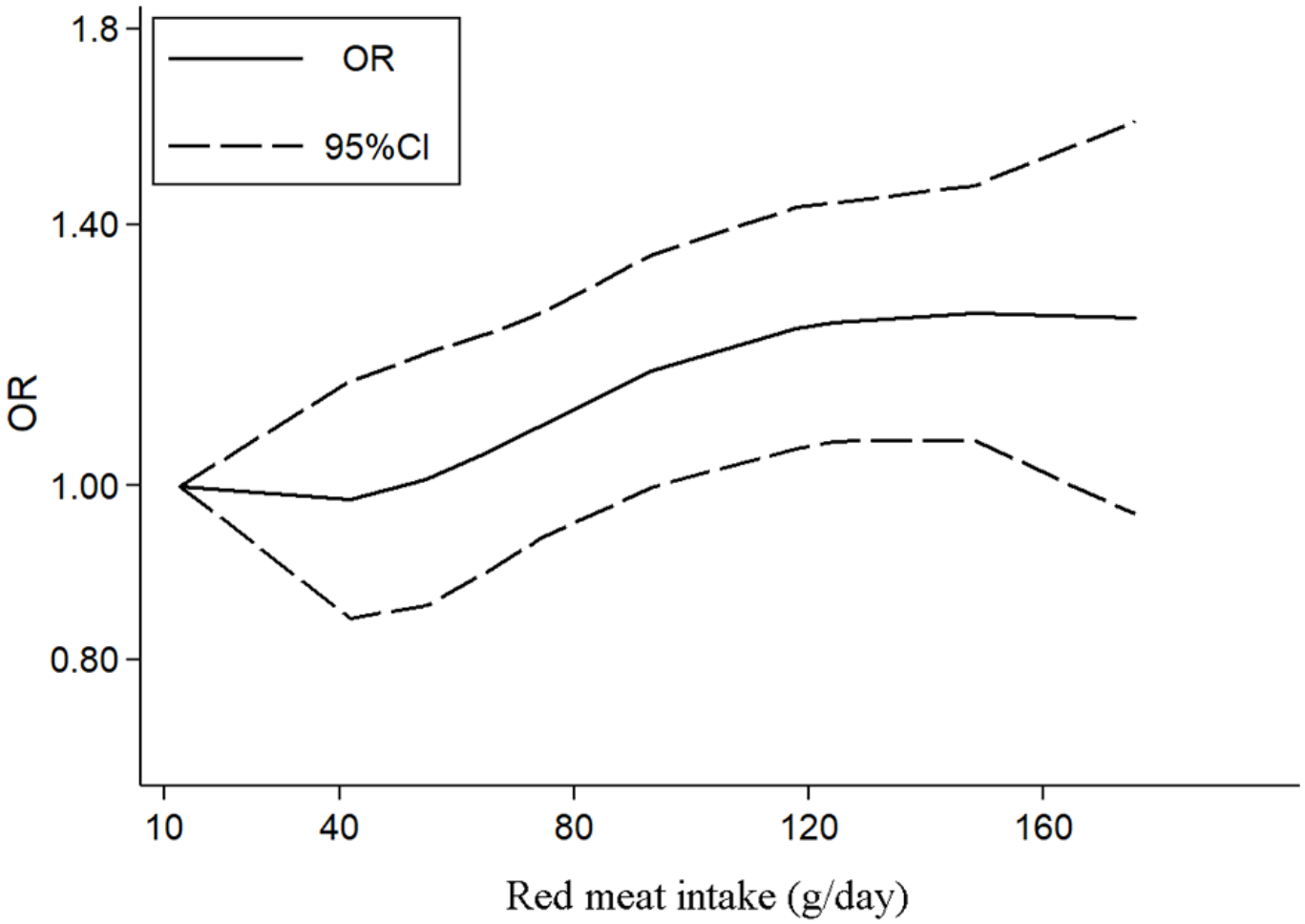

Figure 3

Dose-response relationship between red meat and risk of RA.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx