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Handgrip and knee extension strength as predictors of cancer mortality: a systematic review and meta-analysis

Running head: Muscular strength role in cancer mortality

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ABSTRACT

The specific role of different strength measures on mortality risk needs to be clarified in order to gain a better understanding of the clinical importance of different muscle groups, as well as to inform intervention protocols in relation to reducing early mortality. The aim of the systematic review and meta-analysis was to determine the relationship between muscular strength and risk for cancer mortality. Eligible cohort studies were those that examined the association between muscular strength, as assessed

using validated tests, and cancer mortality in healthy youth and adults. The hazard ratio (HR) estimates obtained were pooled using random effects meta-analysis models. The outcome was cancer mortality assessed using the HR (cox proportional hazards model). Eleven prospective studies with 1,309,413 participants were included and 9,787 cancer-specific deaths were reported. Overall, greater handgrip (HR=0.97, 95% CI, 0.92–1.02; P=0.055; I^2=18.9%) and knee extension strength (HR=0.98, 95% CI, 0.95–1.00; P=0.051; I^2=60.6%) were barely significant associated with reduced risk of cancer mortality. Our study suggests that higher level of muscular strength is close to being statistically associated with lower risk of cancer mortality.

Key words: cancer mortality; muscular strength; fitness; meta-analysis; apparently healthy population

INTRODUCTION

The assessment of muscular strength has been suggested as a useful indicator of functional fitness and health status, given its association with morbidity and mortality [1]. Muscle strength is known to decline with age, and is accompanied by a loss of muscle mass and increase in fat mass [2]. Two studies have reported an association between muscular weakness and cancer-related mortality [3, 4]; however, others have found no association [5, 6]. The underlying mechanisms linking strength preservation with better health outcomes are poorly understood. Nevertheless, the association persists after adjustment for body size and does not appear to be explained by nutritional status, the presence of chronic disease, or level of physical activity participation.

While a primary focus of epidemiologic investigations concerning cancer mortality has been on physical activity participation [7] or cardiorespiratory fitness [8], less is known about the role of muscle strength preservation. Exercise-induced adaptations and functional preservation during cancer treatments may attenuate some of their negative side effects, and also could improve the quality of life for cancer survivors and, as consequence, may even increase long-term survival [9]. Despite the known links between weak handgrip strength and all-cause mortality [10], only a single meta-analytic approach to date has been used to examine its effects (handgrip strength) on cancer mortality rate [11]. However, what remains to be determined is the specific role of different strength measures on cancer mortality in order to gain a better understanding

of the clinical importance of different muscle groups, as well as to inform intervention protocols in relation to reducing early cancer mortality risk.

Therefore, the aim of this systematic review and meta-analysis was to synthesize the association between muscular strength and risk for cancer mortality.

MATERIALS AND METHODS

A systematic review and meta-analysis was conducted following the guidelines of the Cochrane Collaboration. Findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. The review was registered in PROSPERO (Registration number: CRD42016032733).

Data Sources and searches

Two authors (AG-H & RR-V) systematically searched MEDLINE, EMBASE and SPORTDiscus databases from their inception until 01 September 2017 (Supplementary Table 1). The following terms were used (MeSH Terms): muscles OR muscle strength OR muscular OR strength OR obesity OR risk factors AND mortality OR survival rate OR cancer mortality. Only published articles in the English-language were included in the study. In addition, the literature search was supplemented through the manual review of reference list of selected articles.

Eligibility criteria

The *a priori* inclusion criteria are the following:

Design

- Prospective cohort studies.

Participants

- Healthy youth and adults excluding studies in which all patients had chronic diseases such as diabetes, heart failure, hypertension, peripheral artery disease, chronic obstructive pulmonary disease, cancer and patients with critical illness (i.e., we excluded clinical studies of patient groups)

Exposure

- Direct measurement of muscular strength using a validated strength test (e.g., handgrip strength test, etc.).

Outcome measure

- Cancer mortality as assessed using the hazard ratio (HR - cox proportional hazards model).

Two authors (AG-H & RR-V) independently assessed the electronic search results and disagreements were resolved by consensus (FL). Reasons for exclusion of identified articles were recorded in all cases.

Data collection process and data items

Extracted data included the first author's name, year of publication, enrollment year, sex of the sample, duration of follow up, study location, sample size, age at baseline year, HR (and respective 95% CIs), model covariates, muscular strength assessment method, and outcome of interest and cases of cancer mortality. When there was insufficient information, the relevant corresponding author was contacted.

Risk of bias in individual studies

An assessment of each study's quality was made using an adjusted format of the Newcastle–Ottawa quality assessment scale [13]. This scale contains eight items categorized into 3 domains (selection, comparability, and exposure). A point system was used to enable semi-quantitative assessment of study quality, such that the highest-quality studies were awarded a maximum of 1 point per item with the exception of the comparability domain, which allowed allocating 2 points. Thus, the score ranged from 0 to 9 points.

Summary measures

All analyses were carried out using STATA (version 14.0, STATA Corporation, College Station, Tex). HRs with associated 95% confidence intervals (CIs) from studies for each outcome of interest were extracted (used to estimate the risk for mortality), and pooled HRs using random effects (DerSimonian and Laird) models were then calculated. The likelihood approach with random effects was used to better account for the inaccuracy in the estimate of between-study variance [14].

Synthesis of results

The percentage of total variation across the studies due to heterogeneity (Cochran's Q-statistic) [15] was used to calculate the I^2 statistics, considering I^2 values of <25%, 25–50%, and >50% as small, medium, and large amounts of heterogeneity respectively [16].

Influence analyses were conducted to assess the robustness of the summary estimates in order to determine whether any individual study accounted for the heterogeneity. Thus, each study was deleted from the model once in order to analyze the influence of each study on the overall results.

Risk of bias across studies

Small-study effects bias was assessed using the extended Egger's test [17], and presence of publication bias was investigated graphically by examining funnel plots.

Subgroup analysis

Subgroup moderator analyses were conducted to determine whether muscular strength differed according to sex or type of muscular strength assessment test, by stratifying meta-analyses by each of these factors. Therefore, we performed a meta-analysis by subgroups as defined with each measurement criterion. Also, random-effects meta-regression analyses were used to separately evaluate whether results were different by mean age of participants at baseline [18]. A P -value <0.05 was considered statistically significant.

RESULTS

Study selection

The electronic search strategy retrieved 1,126 articles. After removing duplicate references and studies whose not meet inclusion criteria, only 13 articles were screened for eligibility based on title and abstract. The reason for exclusion based on full text review was due to duplicate data (1 study) [4, 19] or analysis used (non cox proportional hazards model) [5]. Finally, 11 original prospective cohort studies met our inclusion criteria and were included in the meta-analysis (Figure 1).

Figure 1 about here

Study characteristics

Table 1 summarizes the characteristics of the eleven included studies [3, 19-27]. All of them were prospective observational studies, and were published from 2007 to 2017. The eleven studies included a total of 1,309,413 participants. Sample sizes ranged from 600 [24] to 1,142,599 participants [22]. All studies reported a combined 9,787 cancer-

specific deaths. The age at cohort enrollment ranged from 16 [22] to 80 years [23]. Studies were conducted in the USA [19, 28], Sweden [22], Japan [20, 23, 24, 26], Norway [25, 27], and 17 high-income, middle-income, and low-income countries [21]. The follow-up duration ranged from four years [23] to 24.2 years [22].

Table 1 about here

Muscle strength tests

Eight studies assessed the muscular strength using the handgrip test [20-27]. The assessment consisted of three attempts with dominant [21, 25] or non-dominant hand [25], two attempts (dominant hand) [23, 24, 26, 27] and averaging both hands [20, 21, 23, 24]. The highest [20, 23, 24, 26, 27] or mean [21, 25] value was used for the analyses expressed as kilograms.

In the remaining studies, muscular strength was assessed using a variety of test protocols. Four studies used a dynamometer to assess isokinetic knee extension strength [23, 24, 28]. One study [22] assessed knee extension, handgrip, and elbow flexion strength. Ruiz et al. [19] assessed upper body strength with a one repetition maximum supine bench press, and lower body strength with a one repetition maximum seated leg press. Low and high muscular strength were determined using each study's population distribution (i.e., quartiles, quintiles). All the studies except one adjusted the estimates by age, tobacco use [20] or body mass index [22], respectively.

Risk of bias within studies

All studies met at least seven of the Newcastle–Ottawa quality assessment criteria except one [3], and were considered to have adequate methodological quality. The studies' score ranged from eight to nine, with a mean total score of 8.7 (Supplementary Table 2).

Meta-analysis

Fig. 2 depicts the pooled HR forest plot of low (reference) versus high muscular strength based on the handgrip strength assessment. The pooled HR of cancer mortality via handgrip strength test was 0.97 (95% CI, 0.92–1.02; $P = 0.055$), with low heterogeneity ($I^2 = 18.9$ %) (Figure 2). When we analyzed cancer mortality risk in relation to knee extension strength, the pooled HR was 0.98 (95% CI, 0.95–1.00; $P = 0.051$) ($I^2 = 60.6\%$) (Figure 3).

Figure 2 about here

Figure 3 about here

Meta-regression analyses plotting age mean shows that there were no observe significant effects on the HR estimates (P = 0.101 and P = 0.982, for handgrip and knee extension, respectively).

Publication bias and sensitivity analysis

When the impact of individual studies was examined by removing studies from the analysis one at a time, we observed that the pooled HR estimate for low muscular strength remained unchanged. There was no indication of study bias (Egger test; P = 0.257 and P = 0.121, for handgrip and knee extension, respectively). Also, the funnel plot for the relationships of handgrip strength with cancer mortality was not asymmetric, thus indicating no issues of bias (Supplementary Figure S1). We have not included a funnel plot for knee extension strength due to should be used only when there are at least 10 studies included in the meta-analysis.

DISCUSSION

Our meta-analysis shows that low muscular strength is barely significant associated with the risk of cancer mortality. Also, the age at baseline was not significant moderator of muscular strength on cancer mortality; however, there was a trend (muscular strength is less protective in older individuals). It is necessary to take into consideration that the prospective design of the study not allow to know whether improved muscle strength prevents cancer development or improves survival with cancer.

To date, few studies have examined the association between muscular strength and cancer mortality and findings have been inconsistent. Our meta-analysis included eleven prospective cohort studies and most reported no significant association between muscular strength and cancer mortality, except for three studies [3, 19, 28]. In a national cohort of people aged 65 and older from the UK, Gale et al. [3] showed that weaker handgrip strength (per SD increase in grip strength) predicted increased cancer mortality in men (HR=0.81, 95% CI 0.70 – 0.95), but not in women. In that study the authors hypothesized that the influence of muscular strength on survival may be more closely related with the muscle functional status in men rather than with muscle size. Similarly,

Sasaki and colleagues [6] found that stronger handgrip was associated with lower cancer mortality, but only in men. The PURE study included 139,691 men and women aged 35-70 years old from 17 different countries and reported and inverse correlation between high grip strength and low cancer mortality only in high-income countries, not in middle- and low-income countries [21]. Meanwhile, another study included young Swedish men aged 16 to 19 years; the followed-up for 24 years indicating that the oldest subjects were 43 years old at the time of analyses and thus probably too young for analyzing the risk of cancer mortality [22].

However, the pooled data included in our meta-analysis that used handgrip testing to assess muscle strength showed barely significant association with cancer mortality. The fact that these studies only assessed muscular strength in small muscle groups (i.e., forearms) may have masked the association between strength and morality. Although handgrip strength has a moderate-to-high correlation with total muscle strength, particularly in youth and young adults [29], the correlation between handgrip strength and strength in larger muscle groups (e.g., low-body muscle) is less robust among older adults [30]. It is also possible that obesity may have confounded our results, as greater body mass is highly associated with grip strength. Indeed, previous studies have demonstrated the role of higher body mass adjusted handgrip strength as a predictive factor for reduced cardiometabolic diseases and disability [31], as well as early mortality [32].

Findings from two studies [19, 28] indicate that muscular strength measurements should represent musculature involved with activities of daily living, such as getting up, lifting or carrying things. In a prospective cohort of 8,677 men, aged 20 to 82 years, Ruiz and colleges [19] reported that higher levels of muscular strength, assessed with an index combining 1-repetition maximal measures for leg and bench press, are associated with lower cancer mortality risk. Surprisingly, a recent study published by Dankel and colleges [28] using the 1999-2002 NHANES data also suggested that individuals in the upper quartile for knee extension muscle were at a 50% reduced risk, however the limited number of deaths due to cancer (n=160) favors high dispersion in the results (HR=0.50, 95% CI 0.29 – 0.85) and increased heterogeneity in our pooled results. Given that specific cancer types have distinct etiologies, the biologic pathways through which low muscular strength influences risk of one type of cancer may differ from the pathogenesis and disease progression of other cancers [33]. Therefore, more studies are

needed in order to better understand the role of muscle strength preservation, and resistance exercise interventions for treatment by cancer subtypes.

A primary strength of our study is that we included data from large populations, including high-quality prospective studies with a mean follow up greater than 10 years (mean 12.8 years), representing various countries, ethnic origins, and socioeconomic backgrounds. However, there are some limitations that should be considered when interpreting these results. First, although all of the included studies had prospective follow-up designs, they are not free of the inherent limitations for cohort studies, which ultimately prevented us from making definitive conclusions about the causal role of muscular strength in cancer mortality. Second, although potential confounders were controlled for in all studies, we cannot exclude the possibility that residual confounding underlies the association between strength and cancer mortality. Indeed, we were unable to determine whether other competing risks or unmeasured confounding (i.e., other lifestyle risk factors, comorbidities or socioeconomic status) may have influenced the observed association of muscular strength with death [34]. Third, due to a lack of available data, we were unable to calculate cancer-specific summary measures of association. Fourth, due to the wide follow-up duration range of 4 to 24.2 years, and the fact that muscle strength does not remain stable over time, this variability in follow-up could certainly influence the effect of baseline strength on cancer mortality. Finally, the categorization of muscular strength in the studies was heterogeneous and may have led to overestimation of the reported associations; also differences in sex distribution and/or cancer type among studies may be behind discrepancies regarding cancer mortality.

In summary, our study demonstrated that higher level of muscular strength was barely significant associated with lower risk of cancer mortality. Also, these results should be cautiously interpreted because some potential heterogeneity-related concerns limit their generalizability. Further studies are needed to identify a plausible biological link between strength preservation and the risk of dying from cancer, as well as to determine the extent to which resistance exercise may benefit specific cancer subtypes.

PERSPECTIVE

Previous meta-analyses have reported that muscle strength is a predictor of all-cause mortality [10] and cardiovascular disease mortality [11] in community-dwelling populations. The current study reported that higher level of muscular strength was barely significant associated with lower risk of cancer mortality. The mechanisms that muscular strength

is strongly associated with all-cause and cardiovascular disease mortality and slightly with cancer mortality need to be explored in further studies. Despite these lightweight associations, muscular strength could be easily and universally applied to identify frail people at increased risk of premature cancer mortality.

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Figure legend

Figure 1. Flow chart of studies included.

Figure 2. Forest plot showing the hazard ratios of cancer mortality comparing low (reference) versus high handgrip strength.

Figure 3. Forest plot showing the hazard ratios of cancer mortality comparing low (reference) versus high knee extension strength.

Table 1. Characteristics of included studies.

Authors, year, country	Sex	Sample size	Age, y (mean or range)	Men, %	Follow-up, y	Muscle strength tests	Adjusted for	Number of deaths
Dankel et al. 2007, USA	Men and women	2773	65.0	49.6	9.7	Knee extensión	Self-reported aerobic-based physical activity, age, race/ethnicity, total colesterol, mean arterial pressure, body mass index, C-reactive protein, self-reported smoking status, use of ambulatory device, statin medication, arthritis, congestive heart failure, coronary artery disease, cancer, diabetes, and stroke	160
Gale et al. 2007, UK	Men and women	800	74.5	56.5	24.0	Handgrip strength	Age	425

Authors, year, country	Sex	Sample size	Age, y (mean or range)	Men, %	Follow-up, y	Muscle strength tests	Adjusted for	Number of deaths
Karlsen et al. 2017, Norway	Women	2529	72.6	0	15.6	Handgrip strength	Age, BMI, smoking, alcohol consumption, hypertension, blood pressure medication, diabetes, family history of myocardial infarction, physical activity and chair-test performance	295
Kishimoto et al. 2014, Japan	Men and women	2527	≥40	42.1	19.0	Handgrip strength	Age, systolic blood pressure, use of antihypertensive agents, diabetes, total cholesterol, BMI, electrocardiogram abnormalities, smoking, alcohol intake and physical activity	249

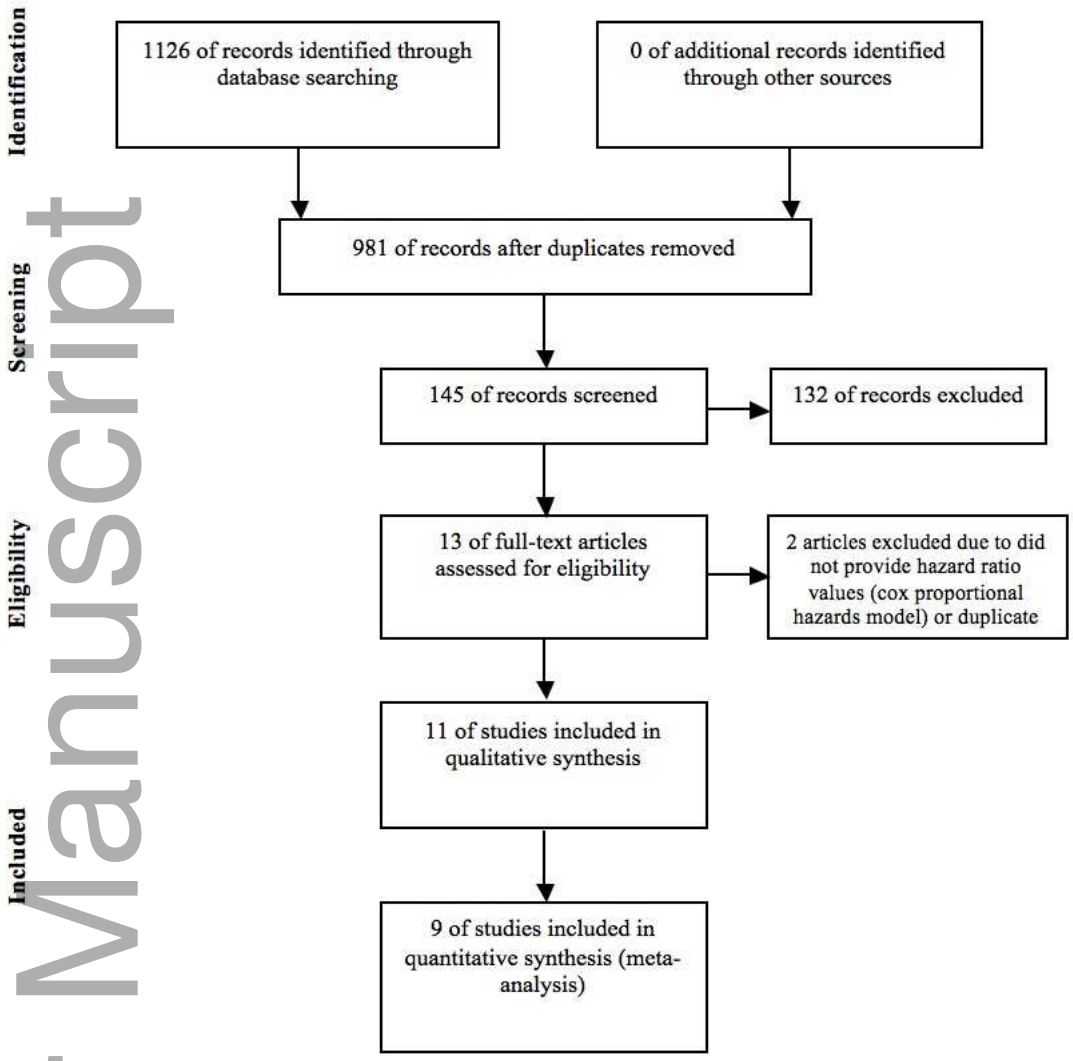
Authors, year, country	Sex	Sample size	Age, y (mean or range)	Men, %	Follow-up, y	Muscle strength tests	Adjusted for	Number of deaths
Leong et al. 2015, 17 countries[a]	Men and women	139691	35-70	41.9	4.0	Handgrip strength	Age, gender, education, employment status, physical activity, tobacco and alcohol use, daily dietary energy intake, proportion of caloric intake from protein, self-reported hypertension, diabetes, heart failure, coronary artery disease, and chronic obstructive pulmonary disease, and self-reported prior stroke or cancer, BMI, and waist-to-hip ratio	2293

Authors, year, country	Sex	Sample size	Age, y (mean or range)	Men, %	Follow-up, y	Muscle strength tests	Adjusted for	Number of deaths
Nofuji et al. 2016, Japan	Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study on Aging	1085	72	42.5	10.3	Handgrip strength	Age, gender, study area, education, body mass index, stroke, heart disease, hypertension, diabetes mellitus, cystatin C, IL-6, high-sensitivity c-reactive protein, albumin, hemoglobin, total cholesterol, self-rated health, depressive mood, smoking, alcohol, physical activity, walking speed and standing balance	324
Ortega et al. 2012, Sweden	Men	1142599	16-19	100	24.2	Knee extensión, handgrip and elbow strength	Birth cohort, conscription age, and conscription office	3425

Authors, year, country	Sex	Sample size	Age, y (mean or range)	Men, %	Follow-up, y	Muscle strength tests	Adjusted for	Number of deaths
Ruiz et al. 2009, USA	Men	8677	42.3	100	18.9	Maximal leg and bench press strength	Age, physical activity, smoking, alcohol intake, BMI, baseline medical conditions, family history of cardiovascular disease, and cardiorespiratory fitness	211
Strand et al. 2016, Norway	Tromsø Study	6850	62	41.7	17.0	Handgrip strength	Adjusted for age, gender, BMI, height, systolic blood pressure, total cholesterol, triglycerides, self-reported general health status, self-reported history of heart attack, stroke, angina, asthma and diabetes, self-reported blood pressure treatment, smoking, leisure-time physical activity and education	2338

Authors, year, country	Sex	Sample size	Age, y (mean or range)	Men, %	Follow-up, y	Muscle strength tests	Adjusted for	Number of deaths
Takata et al. 2007, Japan	Men and women	1282	≥50	39.7	4.0	Knee extension and handgrip strength	Gender, smoking, BMI, systolic blood pressure, marital status, levels of total serum cholesterol or glucose, or complications from prevalent diseases	27
Takata et al. 2012, Japan	Men and women	600	70.0	51.0	10.0	Knee extension and handgrip strength	Gender, BMI, serum level of total cholesterol, smoking, and history of cardiovascular diseases	40

NA=not available, BMI, body mass index. [a] Canada, Sweden, United Arab Emirates, Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey, China, Colombia, Iran, Bangladesh, India, Pakistan, and Zimbabwe.



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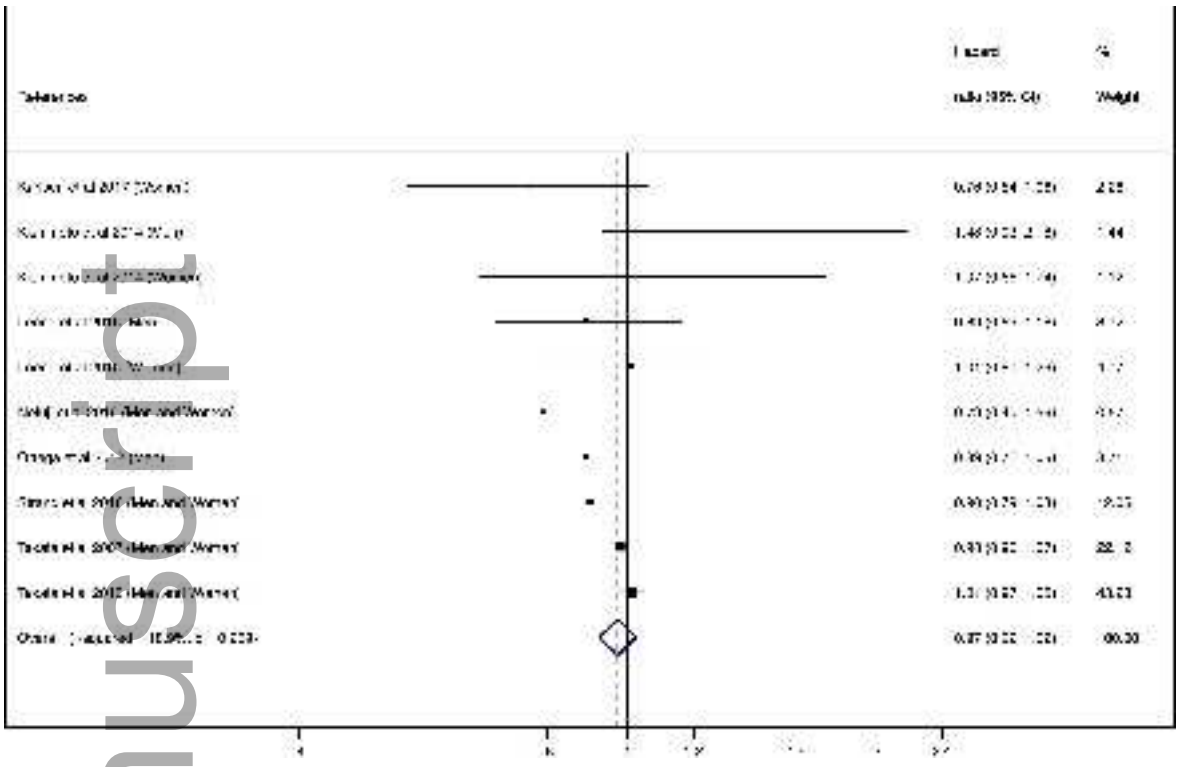

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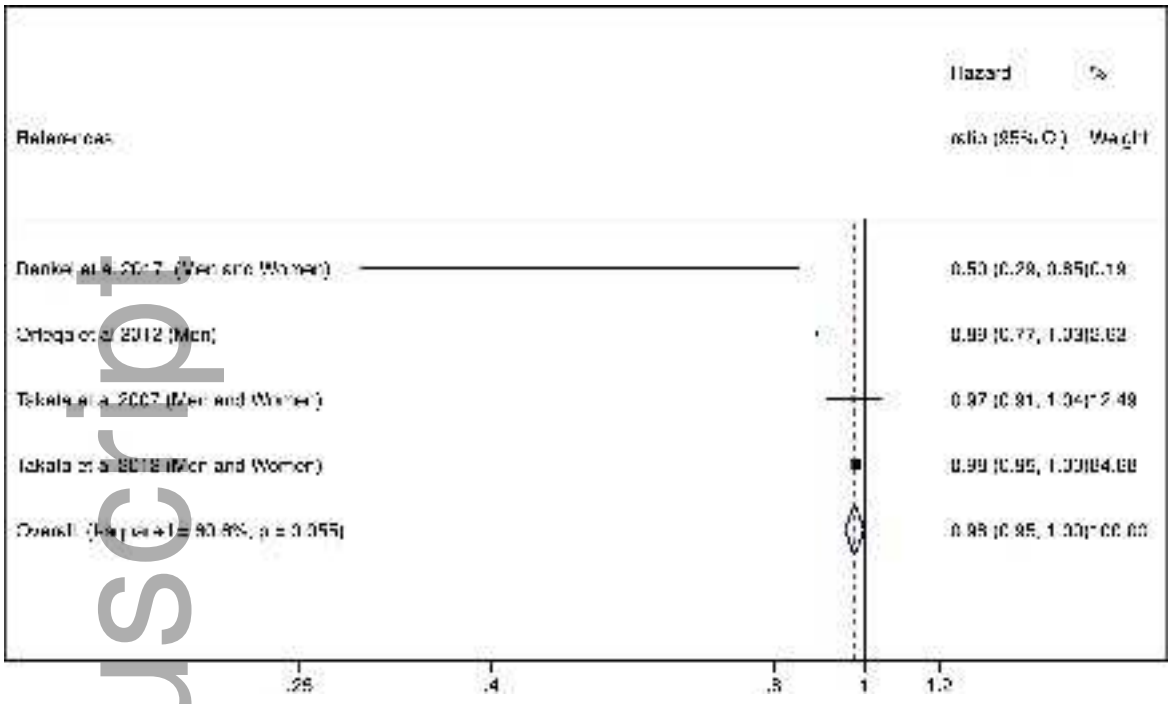

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