International Journal of Cardiology 176 (2014) 680–686

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: A systematic review and meta-analysis

Chun Shing Kwok [a,*,1], Saadia Umar [b,1], Phyo K. Myint [c,1], Mamas A. Mamas [d,1], Yoon K. Loke [e,1]

[a] Cardiovascular Institute, University of Manchester, Manchester, UK
[b] Central Manchester Foundation Trust, Manchester, UK
[c] School of Medicine & Dentistry, University of Aberdeen, Foresterhill, Aberdeen, UK
[d] Cardiovascular Institute, University of Manchester, Manchester, UK
[e] Norwich Medical School, University of East Anglia, Norwich, UK

ARTICLE INFO

Article history:
Received 8 May 2014
Accepted 24 July 2014
Available online 4 August 2014

Keywords:
Vegetarian
Cardiovascular disease
Ischaemic heart disease
Stroke
Mortality

ABSTRACT

Background: Dietary interventions are an important component of cardiovascular risk factor management although their impact on cardiovascular risk and mortality remains uncertain. We have studied influence of a vegetarian diet on cardiovascular risk and mortality.

Methods: We searched MEDLINE and EMBASE for comparative studies that evaluated clinical outcomes associated with vegetarian diet as compared to non-vegetarian controls or the general population. Relevant studies were pooled using random effects meta-analysis for risk of death, ischaemic heart disease (IHD) and cerebrovascular disease. We conducted subgroup analysis according to specific type of cohort (e.g. Seventh Day Adventist [SDA]) and gender.

Results: Eight studies met the inclusion criteria with 183,321 participants (n = 183,321). There was significant heterogeneity in all the meta-analyses, particularly evident with the studies of SDA. In all instances, we found that SDA studies showed greater effect size as compared to non-SDA studies: death (RR 0.68 95% CI 0.45–1.02 vs RR 1.04 95% CI 0.98–1.10), ischaemic heart disease (IHD) (RR 0.60 95% CI 0.43–0.80 vs RR 0.84 95% CI 0.74–0.96) and cerebrovascular disease (RR 0.71 95% CI 0.41–1.20 vs RR 1.05 95% CI 0.89–1.24). Sex specific analyses showed that IHD was significantly reduced in both genders but risk of death and cerebrovascular disease was only significantly reduced in men.

Conclusions: Data from observational studies indicates that there is modest cardiovascular benefit, but no clear reduction in overall mortality associated with a vegetarian diet. This evidence of benefit is driven mainly by studies in SDA, whereas the effect of vegetarian diet in other cohorts remains unproven.

1. Introduction

Cardiovascular disease is the leading global cause of death. In 2008, 7.3 million people died of ischaemic heart disease (IHD) and 6.2 million died from stroke [1]. Diet represents an important risk factor for cardiovascular disease because it is modifiable and it impacts other cardiovascular risk factors such as hypertension [2], obesity [3] and diabetes [4].

Vegetarian diet appears to be associated with favourable effects on cardiovascular health [5]. A recent meta-analysis of seven clinical trials and 32 observational studies found that vegetarian diet was associated with 4.8 mm Hg to 6.9 mm Hg reduction in systolic blood pressure [6]. Another meta-analysis of 12 studies with 1300 participants showed a significant reduction of 1.28 mmol/L in plasma triglyceride level with a vegetarian diet [7]. In addition, the vegetarian diet seems to be protective against obesity, with evidence of a five unit decrease in BMI in vegetarians compared to non-vegetarian in a study involving Seventh Day Adventists (SDAs) [8]. Cohort studies have also shown that vegetarian diet was associated with a significant reduction in prevalence of diabetes and impaired fasting glucose [9] as well as incident diabetes [10].

Previous reviews have evaluated the risk of adverse cardiovascular events with vegetarian and non-vegetarian diets. Key et al. [11] combined the data from five prospective studies and Huang et al. [12] conducted a meta-analysis of seven studies and both found similar reduction in ischaemic heart disease mortality but not in all-cause and cerebrovascular mortality. One important issue is whether any of the positive findings might actually turn out to be specific to Seventh Day Adventists who have lifestyles that may confer cardiovascular or mortality benefit beyond that derived from the vegetarian diet alone. Previous studies have not evaluated the influence of SDA subgroups of vegetarians specifically on CV outcomes. Since these individuals

* Corresponding author at: Institute of Cardiovascular Sciences, University of Manchester, Manchester Royal Infirmary, Manchester M13 9WL, UK. Tel.: +44 161 276 8666; fax: +44 161 2767956.
E-mail address: shingkwok@doctors.org.uk (C.S. Kwok).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2014.07.080
0167-5273/

also have important lifestyle modifications that may also impact on CV outcomes and so may potentially confound previous analysis. Since these studies the Adventist Health Study-2 with 73,000 participants has been published, thus representing a substantial new contribution to the literature [13]. The addition of this new study, as well as further published data from EPIC-Oxford [14] enables more detailed evaluation as to whether the vegetarian diet is truly beneficial across subgroups of the population.

The aim of this systematic review is to update the current understanding of the risk of vegetarian diet and the risk of adverse cardiovascular mortality. In addition, another objective of this study is to determine if the relationship between CV outcomes and diet is gender specific and whether there are differences in risk estimates among Seventh Day Adventist and non-Adventist cohorts.

2. Methods

We conducted a systematic review and meta-analysis of vegetarian diet and risk of all-cause and cardiovascular mortality.

2.1. Search strategy

We searched MEDLINE and EMBASE from inception up to March 2014 (Ovid) with no language limitations using the broad free-text and indexing search terms "vegetarian OR vegan OR plant based diet" AND "acute coronary syndrome OR myocardial infarction OR heart disease OR coronary artery disease OR stroke OR cerebrovascular disease OR cerebrovascular accident OR mortality OR death." In addition, we signed up with PubMed to receive automated electronic notifications for any new articles containing the 'vegetarian'. Bibliographies of included studies and review articles were checked for additional studies.

2.2. Study inclusion criteria

We selected randomised trials and controlled observational studies (case–control or cohort design) that evaluated the association of vegetarians and non-vegetarians and cardiovascular disease and mortality. The following criteria were used for inclusion:

1. Studies with one group of participants designated as vegetarian, non-meat eaters or other groups (priests, monks, SDA, etc.) which are non-meat eaters
2. Control group which could either be the general population, or meat eaters within the same healthcare setting/community
3. Aimed to evaluate one of the following outcomes: myocardial infarction/ischaemic heart disease (IHD)/coronary heart disease, stroke/cerebrovascular disease or all cause/IHD/cerebrovascular disease related mortality.

There were no restrictions on the type of vegetarian or any restriction on the non-vegetarian control group. In addition, there was no restriction based on language, design (prospective or retrospective), sample size or other methodologies.

2.3. Study selection and extraction

Two authors (CSK and SU) independently screened titles and abstracts of studies found on the search for potentially relevant studies. Any uncertainty about inclusion was resolved by a third review (MAM or YKL). The potentially relevant studies were downloaded and their full texts were reviewed for final inclusion. Data was extracted by two authors (CSK and SU) onto pre-specified tables that included elements on study design, participants, participant selection criteria and results (including statistical adjustment). The data extracted was then checked (in an unblinded manner) by at least one other reviewer (MAM or YKL).

2.4. Quality assessment

The quality of the studies was determined by considering the ascertainment of dietary intake, ascertainment of outcomes, lost to follow-up, use of propensity matching or adjustments and generalisability of the findings. Studies of the general population were considered to be generalisable while studies of unique cohorts such as SDA, priests or monks were not generalisable. Risk of bias overall was considered to be low, moderate or high depending on the extent to which the quality assessment criteria were fulfilled. If there were >10 studies available in the meta-analysis, with no evidence of substantial statistical heterogeneity, we aimed to generate funnel plots to assess the possibility of publication bias [15].

2.5. Data analysis

Data analysis was performed using RevMan 5.2 (Nordic Cochrane Centre). Random effects meta-analysis was performed using the inverse variance method. We chose to pool the adjusted results where available to reduce the risk of confounded results. We assumed similarity between the odds ratio and other relative measures such as relative risk, rate ratios or hazard ratios because cardiovascular events and death were rare events [16]. Statistical heterogeneity was assessed using I^2 statistic [17], with I^2 values of 30–60% representing a moderate level of heterogeneity. Pre-specified sensitivity analysis was performed by evaluating the effect of gender and cohort with and without SDA.

3. Results

3.1. Study selection

Eight studies met the inclusion criteria and one of these studies was not included in the primary analysis because it was deemed to have a high risk of bias [18]. The reason for the high risk of bias classification was because not all participants completed the dietary questionnaire and some participants had mixed diets. The results were not adjusted for confounders and there was poor generalizability and comparability because the vegetarian group was a cohort of Japanese priests whose mortality rate was judged against the general male population. The process of study selection is shown in Fig. 1.

3.2. Study characteristics

The designs and participant characteristics of included studies are shown in Table 1. There were six prospective cohort studies [13,14,19–22] and two observational cohorts where it was not clear if their design was prospective or retrospective [18,23]. The total number of participants was 183,321. These studies took place between 1955 and 2009 in countries such as the USA, United Kingdom, Germany, Netherlands and Japan. The sample size ranged from 1904 to 73,308 and three studies were of SDA cohorts [13,19,23]. The definition of vegetarian, study follow up and results of the studies are shown in Table 2.

3.3. Quality assessment of included studies

The risk of bias was deemed to be moderate in five studies and low to moderate in two studies (Supplementary Table 1). All the studies ascertained the dietary intake of participants by using questionnaires or surveys and the ascertainment of death was reliable using death certificates, ICD codes and death registers. In addition, all studies had some degree of lost to follow-up or exclusions which ranged from 35 participants (0.003%) to 23,161 (24%).

All studies that used adjusted analysis adjusted for age and sex but important confounders may not have been accounted for in some of the studies. Six studies [13,14,19–22] adjusted for potential confounders and the use of adjustment was not clear in two studies [18,23]. Two important factors are BMI and smoking status and only two studies adjusted for BMI [14,20] and five adjusted for smoking status [13,14,20–22]. Four studies [13,18,19,23] were not generalizable to the general population because they were SDA cohorts or cohorts of priests. In addition, the choice of control group is an important consideration. Two studies [18,23] did not have a control group that was non-vegetarian within the same population (Table 3). These studies used standardized mortality rate for the population studied which includes both vegetarians and non-vegetarians as the control group that may bias outcomes.

3.4. Association of vegetarian diet with mortality and vascular events

3.4.1. Death

We included seven cohorts in the pooled analysis. All three Adventist cohorts demonstrated significant associations between vegetarian diet and reduced all-cause mortality, whereas the non-Adventist studies did not show any mortality reduction in vegetarians (Fig. 2). Testing for subgroup differences suggests that the findings in the Adventist cohorts are likely to be significantly different from the other cohorts ($p = 0.05$).

3.4.2. Ischaemic heart disease or cardiac adverse events

We included seven cohorts in the pooled analysis. Two of the three Adventist cohorts demonstrated significant associations between