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REVIEW

The Nordic diet and the risk of non-communicable chronic disease and mortality: a systematic review and dose-response meta-analysis of prospective cohort studies

Yahya Jalilpiran[a,b], Ahmad Jayedi[c,d], Kurosh Djafarian[a], and Sakineh Shab-Bidar[c]

[a]Department of Clinical Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [b]Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences (TUMS), Tehran, Iran; [c]Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [d]Food Safety Research Center (Salt), Semnan University of Medical Sciences, Semnan, Iran

ABSTRACT
We aimed to investigate the association between adherence to the Nordic diet (ND) and the risk of chronic disease. PubMed, Scopus, and ISI Web of Science were searched to February 2020 to find prospective cohort studies. The relative risks (RRs) were calculated using a fixed-effects/random-effects model. The certainty of evidence was rated using the GRADE approach. Thirteen prospective cohort studies with 930,153 participants were included. The RRs for the highest compared to the lowest category of adherence to the ND were 0.78 (95%CI: 0.69, 0.87; $I^2 = 51\%$, $n = 6$) for all-cause mortality, 0.78 (95%CI: 0.74, 0.83; $I^2 = 70\%$, $n = 4$) for cardiovascular mortality, 0.86 (95%CI: 0.80, 0.93; $I^2 = 83\%$, $n = 4$) for cancer mortality, 0.88 (95%CI: 0.79, 0.98; $I^2 = 3\%$, $n = 3$) for stroke, 0.80 (95%CI: 0.68, 0.95; $I^2 = 47\%$, $n = 3$) for myocardial infarction, and 0.90 (95%CI: 0.82, 0.99; $I^2 = 33\%$, $n = 4$) for type 2 diabetes. There was an inverse linear association between the ND score and the risk of mortality, and an inverse monotonic association for type 2 diabetes. The certainty in the estimates ranged from very low to low.

KEYWORDS
Chronic diseases; meta-analysis; mortality; Nordic diet; prospective cohort studies

Introduction

For decades, management of chronic diseases such as the cardiovascular diseases (CVD), type 2 diabetes, cancer, and chronic respiratory diseases has become challengeable for health systems (Vos et al. 2015). Accordingly, the roles of nutritional behaviors, one of the most important modifiable risk factors, in the prevention and treatment of these conditions has received more attention (Kant 2010; Nowson et al. 2018). Previous research in nutritional epidemiology focused on the potential association of individual foods or nutrients with disease risks. However, recent studies highlight dietary patterns-disease relationships because of their simplicity and representatively point of view (Hu 2002). The Nordic diet (ND) is one of these major dietary patterns that its potential association with chronic disease risks have been investigated in recent research (Åkesson et al. 2013; Galbete et al. 2018; Olsen et al. 2011).

The ND first was developed to introduce a dietary approach based on typical Nordic foods consumed in Northern European regions (Uusitupa et al. 2013). This pattern encourages high consumption of some healthy foods such as fruits, vegetables, whole grains, fish, rapeseed oil, and low-fat dairy products; as well as low consumption of processed meat and alcohol (Kanerva, Kaartinen, Schwab, et al. 2014). The beneficial effects of the ND on some cardio-metabolic factors such as systolic and diastolic blood pressure and total and low-density lipoprotein cholesterol have been found in a recent systematic review and meta-analysis of the randomized controlled trials (RCTs; Ramezani-Jolfaie, Mohammadi, and Salehi-Abargouei 2019). Greater adherence to this dietary pattern was also associated with better physical performance in older adults (Perälä et al. 2016).

Several epidemiological studies have investigated the associations between greater adherence to the ND and the risk of all-cause mortality, and death due to cancer and CVD (Kyrø et al. 2013; Roswall, Sandin, Löf, et al. 2015; Tertsunen et al. 2020). Moreover, the associations between the ND and occurrence of some chronic diseases such type 2 diabetes (Galbete et al. 2018; Kanerva, Rissanen, et al. 2014; Lacoppidan et al. 2015), some cancer types (Kyrø et al. 2013; Roswall, Li, et al. 2015), myocardial infarction (Galbete et al. 2018; Gunge et al. 2017), and ischemic heart diseases (Roswall, Sandin, Scragg, et al. 2015) have been investigated previously. However, the results of these studies are inconclusive and there is no agreement of the associations of the ND with the risk of mortality or incidence of chronic diseases. Therefore, we aimed to conduct a dose-

CONTACT Sakineh Shab-Bidar s_shabbidar@tums.ac.ir Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran.No 44, Hojjat-dost Alley, Naderi St., Keshavarz Blvd, Tehran, Iran.

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response meta-analysis on prospective observational studies to test the potential associations between adherence to the ND and the risk of chronic disease in the general population.

Methods

The present research was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement (Moher et al. 2009). The protocol of this study was registered in the center for Open Science Framework (OSF) database (http://www.osf.io, DOI: 10.17605/OSF.IO/5HMJW).

Search strategy

A systematic search was performed in PubMed, Scopus, and ISI Web of Knowledge for identification of potential eligible studies from inception up to February 18, 2020. The following keywords were used: ("Nordic diet" OR "Nordiet" OR "Baltic sea diet" OR "Nordic dietary pattern" OR "Baltic sea dietary pattern"). We used the combination of Medical Subject Headings (MeSH) and non-MeSH terms (Supporting Information Table S1). The search was performed without any restriction in language. The reference lists of the relevant articles were manually searched.

Eligibility and study selection

All articles obtained from the databases were screened and of those, the articles with the following criteria were selected: (a) studies with prospective observational design; (b) studies conducted in the general population aged 18 years and older; (c) reported the adherence to the ND as exposure; (d) reported all-cause and cause-specific mortality or incidence of non-communicable chronic diseases such as CVD, type 2 diabetes, and different cancer types as outcomes; and (e) reported hazard ratio (HR) or relative risk (RR) alongside with 95% confidence interval (CI) across categories of the ND score.

Data extraction and quality assessment

Two independent authors (Y.JP., A.J.) recorded the following characteristics from eligible studies: first author's name, date of publication, study name, country, mean age or age range (year), number of participants, number of cases, dietary assessment method, reported effect estimates and the 95%CI of mortality or incidence of chronic diseases across categories of the ND, and list of confounders adjusted for in the multivariable models. We considered fully adjusted models for reporting effect estimates from each primary prospective cohort study. Study quality assessment was applied with the use of the Newcastle–Ottawa Scale with highly qualified studies received ≥ 7 stars (Stang 2010). Disagreements were resolved through discussion and consensus under supervision of the corresponding author (S.SB).

Statistical analysis

Meta-analysis was conducted if at least two studies reported effect size for the same association. The RR and its 95%CI was considered as the effect size. The reported HRs were considered as equal to RR (Symons and Moore 2002). For the highest versus lowest category meta-analysis, the effect sizes for the highest compared to the lowest categories of adherence to the ND in primary studies were combined using the DerSimonian and Laird random-effects model (DerSimonian and Laird 1986). A fixed-effects model was used to combine study-specific results when less than five studies were present (Borenstein et al. 2011; Tufanaru et al. 2015). If studies reported results separately for men and women, we considered them as two separate cohort studies. To test the potential effect of each primary study on pooled effect size, we performed sensitivity analyses by serial exclusion of each study from the main analyses. We did not perform subgroup analyses due to very low number of studies. Between-studies heterogeneity was assessed using Cochrane's Q test and quantified by I^2 statistic (Higgins et al. 2003). Potential publication bias was not checked due to very low number of primary studies ($n < 10$; Higgins and Wells 2011).

We also performed a dose-response meta-analysis to report the results for each 2-unit increment in adherence to the ND (Berlin, Longnecker, and Greenland 1993; Orsini, Bellocco, and Greenland 2006). A potential non-linear association was also examined by modeling the ND scores using restricted cubic splines with three knots at fixed percentiles (10, 50, and 90%) of the distribution (Orsini et al. 2012). A P-value for non-linearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. The method needs distribution of cases and participants/person years and adjusted RR and its 95%CI across ≥ 3 quantitative categories of the ND score. If the numbers of participants or cases have not been reported in primary studies, we estimated these values by dividing the total number of participants or cases by the number of categories, if the exposure was defined as quantiles (Jayedi, Rashidy-Pour, et al. 2018). For those studies that reported the ND score as categoric and did not use the traditional ND score (ranging from 0 to 6), we transformed the scores to a 6-point scale. For this purpose, to translate the scores from 25-point scale to 6-point scale, we multiplied the median score of each category (in 25-point scale) by 6, divided by 25 (Soltani et al. 2019). For studies in which the reference category was not the lowest one, we recalculated effect sizes taking the lowest category as reference (Hamling et al. 2008). All analyses were conducted with Stata software, version 14 (Stata Corp, College Station, Texas, USA). A P-value <0.05 was considered statistically significant.

Grading the evidence

The certainty in the estimates was assessed by the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (Guyatt et al. 2008). This tool grades the evidence as high, moderate, low, or very low quality. Observational studies such as prospective cohort studies start as low-quality evidence that can be downgraded or upgraded on the basis of pre-specified criteria. The criteria used to downgrade evidence include study limitations (weight of studies showing risk of bias as assessed by the Newcastle Otawa Scale; Guyatt, Oxman, Vist, et al. 2011), inconsistency (substantial unexplained between-study heterogeneity, $I^2 \geq 50\%$ and $P_{heterogeneity} < 0.10$; Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al. 2011), indirectness (presence of population, intervention or comparator factors that limit the generalizability of the results; Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al. 2011), imprecision (Guyatt, Oxman, Kunz, Brozek, et al. 2011), and compelling evidence of publication bias (Guyatt, Oxman, Montori, et al. 2011). To determine if there was imprecision in the estimates, we first considered the optimal information size (the number of cases included in the review compared with the number required by a conventional sample size calculation for a single adequately powered trial). On the basis of a 5% event rate in the control group and a 25% RR reduction, we calculated the optional information size to be 400 cases (Mayhew et al. 2016). We also rated down for imprecision when the 95%CI include 1.00 and the upper or lower bounds of 95%CI was <0.8 and >1.2, respectively. The criteria used to upgrade the certainty of evidence include a large magnitude of association, a dose–response gradient, and attenuation by plausible confounding.

Results

Literature research

Our systematic and hand searches resulted in identification of 564 studies. After removing duplicates and screening the title and abstract, 367 studies were excluded. Twenty-eight full texts were fully reviewed for eligibility. Of those, 14 studies were excluded because of the following reasons: two studies were not performed in the general population (Hillesund et al. 2014; Puaschitz et al. 2019; Ratjen et al. 2017), one study had cross-sectional design (Kanerva et al. 2013), two studies assessed changes in body weight and waist circumference during follow-up period (Kanerva et al. 2018; Li, Roswall, Ström, et al. 2015), three studies investigated the incidence of disability (Perälä et al. 2019), sarcopenia (Isanejad et al. 2018), and muscle strength (Perälä et al. 2017) among older adults, two studies evaluated the associations of the ND with telomere length and attrition (Meinilä et al. 2019) and life satisfaction (Isanejad et al. 2019), and four studies were conducted to assess the associations of the ND with the risk of cognitive decline (Shakersain et al. 2018), changes in bone mineral density (Erkkilä et al. 2017), prevalence of elevated depressive symptoms (Ruusunen et al. 2013), the risk of periodontal disease development (Jauhiainen et al. 2020; Supporting Information Figure S1), accordingly 14 studies received inclusion criteria. Of those, only one study reported risk of breast cancer as outcome and did not include in final analyses (Li, Roswall, Sandin, et al. 2015). Finally, 13 prospective cohort studies with 50,471 cases among 930,153 participants were considered eligible for the analyses (Galbete et al. 2018; Gunge et al. 2017; Hansen et al. 2017; Kanerva, Rissanen, et al. 2014; Kyrø et al. 2013; Lacoppidan et al. 2015; Lassale et al. 2016; Lemming et al. 2018; Olsen et al. 2011; Roswall, Li, et al. 2015; Roswall, Sandin, Löf, et al. 2015; Roswall, Sandin, Scragg, et al. 2015; Tertsunen et al. 2020). Included studies assessed the association of the ND with the risk of mortality due to all-cause (Lassale et al. 2016; Lemming et al. 2018; Olsen et al. 2011; Roswall, Sandin, Löf, et al. 2015; Tertsunen et al. 2020), total CVD (Lassale et al. 2016; Lemming et al. 2018; Roswall, Sandin, Löf, et al. 2015; Tertsunen et al. 2020), and total cancer (Lassale et al. 2016; Lemming et al. 2018; Roswall, Sandin, Löf, et al. 2015; Tertsunen et al. 2020), as well as the incidence of non-communicable chronic diseases including stroke (Galbete et al. 2018; Hansen et al. 2017; Roswall, Sandin, Scragg, et al. 2015), myocardial infraction (Galbete et al. 2018; Gunge et al. 2017), type 2 diabetes (Galbete et al. 2018; Kanerva, Rissanen, et al. 2014; Lacoppidan et al. 2015), and colorectal cancer (CRC; Kyrø et al. 2013; Roswall, Li, et al. 2015). Three prospective cohort studies reported effect sizes for the relation of the ND with the risk of total cancer incidence (Galbete et al. 2018), CVD events (such as ischemic heart disease, total CVD events, arrhythmias, thrombosis, and hypertensive disease; Roswall, Sandin, Scragg, et al. 2015), and stroke subtypes (hemorrhagic and ischemic stroke; Hansen et al. 2017) that were not included in the analyses. Two included studies also assessed the association of the ND with the risk of mortality due to other diseases (diseases except of CVD and cancer; Tertsunen et al. 2020) and ischemic heart disease (Lemming et al. 2018) that were not included in meta-analysis. In fact, meta-analysis was conducted if at least two studies reported effect size for the same association.

Study characteristics

We included data from 13 prospective cohort studies (50,471 deaths and incidence of chronic diseases among 930,153 participants), that were published from 2011 to 2020 with a follow-up duration ranging from seven to 23.6 year (Table 1; Galbete et al. 2018; Gunge et al. 2017; Hansen et al. 2017; Kanerva, Rissanen, et al. 2014; Kyrø et al. 2013; Lacoppidan et al. 2015; Lassale et al. 2016; Lemming et al. 2018; Olsen et al. 2011; Roswall, Li, et al. 2015; Roswall, Sandin, Löf, et al. 2015; Roswall, Sandin, Scragg, et al. 2015; Tertsunen et al. 2020). Four prospective cohort studies reported sex-specific RRs only that were separately included in relevant analyses (Gunge et al. 2017; Kyrø et al. 2013; Lacoppidan et al. 2015; Olsen et al. 2011). Accordingly, all included studies were conducted in European countries. One study was performed in men (Tertsunen et al. 2020), four studies in women (Lemming et al. 2018; Roswall, Li, et al. 2015; Roswall, Sandin, Löf, et al. 2015; Roswall, Sandin, Scragg, et al. 2015), and other eight studies in both sexes (Galbete et al. 2018; Gunge et al.

Table 1. General characteristics of included studies in the meta-analysis of the Nordic diet and the risk of chronic disease.

Author (ref), year	Study name, country	Age (range; mean, years)	Participants	Outcome(s) (number of cases)	Gender	Follow-up duration (years)	Dietary assessment (no. of ND Components)	Nordic diet score (mean; range)	Comparison	Effect estimate (95%CI) (highest versus lowest category)	Adjustments	Nordic diet components
Tertsunen et al. (2020)	The Kuopio Ischemic Heart Disease Risk Factor Study, Finland	42–60	1547	All-cause mortality (576) CVD mortality (250) Cancer mortality (194)	M	23.6	4-day food records	0–25	Q4 vs. Q1	All-cause mortality 0.78(0.99–0.62) CVD mortality 0.71(1.01–0.50) Cancer mortality 0.79(1.19–0.52)	Age (years), examination year and energy intake, pack-years of smoking, body mass index (kg/m2), leisure-time physical activity (kcal/day), education (years), marital status (yes/no) and income (euros/year).	All fruits, berries Roots, pulses, vegetables Whole grains (rice, pasta) Fat-free milk and milk < 2% fat Salmon, freshwater fish Processed and unprocessed meat Total fat as a percentage of total energy intake Ratio of PUFA to SFA + trans-fatty acids Alcohol
Lemming et al. (2018)	The Swedish Mammography Cohort, Sweden	61 (median)	38,428	All-cause mortality (10,478) CVD mortality (2355) Cancer mortality (3003)	F	17 (median)	FFQ	0–6	High (5–6) vs. low (0–1)	All-cause mortality 0·98 (0.91–1.06) CVD mortality 0.91 (0.79–1.05) Cancer mortality 1.14 (0.97–1.32)	Age, educational level, living alone, physical activity, energy intake, smoking habits, Charlson's comorbidity index, and mMED, energy intake. BMI.	Whole-grain bread Cruciferous vegetables Root vegetables Oatmeal Apples and pears Fish
Galbete et al. (2018)	The EPIC-Potsdam study, Germany	35–65	27548	Type2 diabetes incidence (1376) Myocardial infraction incidence (312) Stroke incidence (321)	M/F	10.6	Self-administered semi-quantitative FFQ	0–18	High adherence vs. Low adherence	Type2 diabetes incidence 1.01(0.87–1.18) Myocardial infraction incidence 0.88 (0.64–1.20) Stroke incidence 0.97 (0.72–1.31)	Age, sex, smoking status, education, total energy (kcal/day), vitamin supplementation, body mass index (kg/m2), waist circumference (cm), cycling, sports, prevalent hypertension (not in the analyses on cancer), alcohol intake (7 categories) (only for the Nordic diet analysis).	Whole grain and rye bread Berries Apples and pears Cabbage and cruciferous Fish Root vegetables Low-fat dairy products Potatoes Vegetable fats (excluding olive oil)
Hansen et al. (2017)	The Danish Diet, Cancer and Health cohort, Denmark	Median age = 56.1	55338	Total stroke incidence (2283)	M/F	13.5 (median)	Semi-quantitative FFQ	0–6	High (4–6) vs. low (0–1)	Total stroke incidence 0.83 (0.73–0.95)	Total energy intake, alcohol intake, physical activity, smoking, education, BMI-adjusted waist circumference, atrial fibrillation (not in the analyses of hemorrhagic stroke), hypertension, hypercholesterolemia, and diabetes mellitus.	Rye bread Cabbage Root vegetables Oatmeal Apples and pears Fish
Gunge et al. (2017)	The diet, cancer and health cohort study, Denmark	50–64	54568	Myocardial infraction incidence (M;1669, F;653)	M/F	13.6 (median)	Semi-quantitative FFQ	0–6	High (5–6) vs. low (0)	Myocardial infraction incidence (M ;0.86 (0.69–1.08), F; 0.56 (0.37–0.83))	Age, time-under-study, schooling, alcohol intake, smoking, time since cessation, participation in sports, processed meat intake, menopausal status, hormone replacement therapy, total energy intake, BMI, waist circumference, systolic blood pressure, self-reported hypertension, hypercholesterolemia, self-reported hypercholesterolemia.	Rye bread Cabbage Root vegetables Oatmeal Apples and pears Fish
Lassale et al. (2016)	European Prospective Investigation into Cancer and Nutrition, (10 European Countries)	50.8	451,256	All-cause mortality (15,200) CVD mortality (3761) Cancer mortality (7475)	M/F	12.8 (Median)	FFQ	0–6	Q4 vs. Q1	All-cause mortality 0.73 (0.70–0.76) CVD mortality 0.71(0.65–0.78) Cancer mortality 0.77 (0.72–0.82)	Adjusted for dietary score and age at baseline, BMI, Physical activity, smoking status and educational level, and stratified by sex and study center.	Whole-grain bread Cruciferous vegetables Root vegetables Oatmeal Apples and pears Fish

(*continued*)

Table 1. Continued.

Author (ref), year	Study name, country	Age (range; mean, years)	Participants	Ouctome(s) (number of cases)	Gender	Follow-up duration (years)	Dietary assessment (no. of ND Components)	Nordic diet score (mean; range)	Comparison	Effect estimate (95%CI) (highest versus lowest category)	Adjustments	Nordic diet components
Roswall, Li, et al. (2015); Roswall, Sandin, Löf, et al. (2015); Roswall, Sandin, Scragg, et al. (2015)	Swedish Women's Lifestyle and Health cohort, Sweden	29–49	43310	Stroke incidence (698)	F	21.3 (Median)	FFQ	0–6	High (4–6) vs. low (0–1)	Stroke incidence 0.98 (0.78–1.22)	Age, smoking status and duration, current tobacco consumption and time since cessation, education and intake of alcohol and processed meats, energy intake, body mass index and doctor-diagnosed hypertension and diabetes.	Cabbage Root vegetables Whole–grain bread Oatmeal Apples and pears Fish and selfish
Roswall. Li, et al. (2015); Roswall, Sandin, Löf, et al. (2015); Roswall, Sandin, Scragg, et al. (2015)	Swedish Women's Lifestyle and Health cohort, Sweden	29–49	44961	All-cause mortality (1855) CVD mortality (270) Cancer mortality (1113)	F	21.3 (Median)	FFQ	0–6	High (4–6) vs. low (0–1)	All-cause mortality 0.82 (0.71–0.93) CVD mortality 0.88 (0.62–1.26) Cancer mortality 0.87 (0.73–1.03)	Age, smoking status, duration, current tobacco consumption, time since smoking cessation, school education, BMI, alcohol intake, red meat intake, processed meat intake, and energy intake.	Wholegrain bread Cabbage Root vegetables Oatmeal Apples and pears Fish and selfish
Roswall, Li, et al. (2015); Roswall, Sandin, Löf, et al. (2015); Roswall, Sandin, Scragg, et al. (2015)	Swedish Women's Lifestyle and Health cohort, Sweden	29–49	45222	Colorectal cancer incidence (314)	F	21.3 (Median)	Web-based FFQ	0 – 6	High (4–6) vs. low (0–1)	Colorectal cancer incidence 1.09 (0.78–1.52)	Age, BMI, education, smoking status, cigarettes/day, time since smoking cessation, and oral contraceptives, alcohol, red/processed meat, energy.	Wholegrain bread Cabbage Root vegetables Oatmeal Apples and pears Fish and selfish
Lacoppidan et al. (2015)	The diet, cancer and health cohort study, Denmark	50–64	55060	Type 2 diabetes incidence (M;4097, F;3269)	M/F	15.3 (Median)	Semi-quantitative FFQ	0–6	High (5–6) vs. low (0)	Type 2 diabetes incidence (M; 0.80 (0.69–0.94), F; 0.89 (0.72–1.10))	Age, schooling level, participation in sports, smoking status, alcohol intake, red and processed meat, total energy intake, body mass index and waist circumference.	Rye bread Cabbage Root vegetables Oatmeal Apples and pears Fish
Li, Roswall, Sandin, et al. (2015); Li, Roswall, Ström, et al. (2015)	The Norwegian-Swedish Women's Lifestyle and Health Cohort Study, Norway	29–49	44296	Breast cancer incidence (1464)	F	20	FFQ	0–6	High (4–6) vs. low (0–1)	Breast cancer incidence 1.08 (0.92–1.27)	Age, BMI, height, education, smoking, cigarettes per day, age at menarche, family history of breast cancer, personal history of benign breast disease, age at first child birth, number of children, breast feeding, oral contraceptives, alcohol, saturated fat intake, and energy intake.	Whole grain bread Oatmeal Apples and pears Cabbages Root Vegetables Fish and shellfish
Kanerva, Kaartinen, et al. (2014); Kanerva, Rissanen, et al. (2014)	The Helsinki Birth Cohort Study, Finland	Not reported	6745	Type 2 diabetes incidence (541)	M/F	10	FFQ	0–25	Q5 vs. Q1	Type 2 diabetes incidence 0.93 (0.72–1.21)	Age and sex, years of education, smoking, physical activity, and intake of energy, abdominal obesity, and intake of vitamin D.	All fruits, berries Roots, pulses, vegetables Cereals (Rye, oats, barley) Fat-free milk and milk < 2% fat Salmon, freshwater fish Processed and unprocessed meat Total fat as a percentage of total energy intake Ratio of PUFA to SFA + trans-fatty acids Ethanol
Kyrø et al. (2013)	The diet, cancer and health cohort study, Denmark	50–64	55880	Colorectal cancer incidence (M; 567, F; 458)	M/F	13)Median(	Semi-quantitative FFQ	0–6	High (5–6) vs. low (0–1)	Colorectal cancer incidence (M; 0.87 (0.61–1.25), F; 0.65 (0.46–0.94))	Alcohol intake, smoking status, use of hormone replacement therapy (women only), schooling, sports, use of non-steroidal anti-	Rye bread Cabbage Root vegetables Oatmeal Apples and pears Fish

(*continued*)

Table 1. Continued.

Author (ref), year	Study name, country	Age (range; mean, years)	Participants	Ouctome(s) (number of cases)	Gender	Follow-up duration (years)	Dietary assessment (no. of ND Components)	Nordic diet score (mean; range)	Comparison	Effect estimate (95%CI) (highest versus lowest category)	Adjustments	Nordic diet components
											inflammatory drugs, waist circumference and meat intake (processed and Red).	
Olsen et al. (2011)	The diet, cancer and health cohort study, Denmark	50–64	50263	Al-cause mortality (M; 2383, F; 1743)	M/F	12	Semi-quantitative FFQ (6)	0–6	High (6) vs. low (1)	Al-cause mortality (M; 0.64 (0.46–0.89), F; 0.75 (0.49–1.15))	Time-dependent variables (age and time under study), smoking status, smoking duration, current tobacco consumption, time since cessation, alcohol intake, school education, participation in sports, time spent on sports per week, BMI, red meat intake, and processed meat intake, total energy intake.	Rye bread Cabbage Root vegetables Oatmeal Apples and pears Fish

BMI: body mass index; CVD: cardiovascular disease; FFQ: food frequency questionnaire; F: female; M: male; MI: myocardial infraction; mMED: modified Mediterranean diet; PUFA: polyunsaturated fatty acid; Q: quartile/quantile; SFA: saturated fatty acid.

2017; Hansen et al. 2017; Kanerva, Rissanen, et al. 2014; Kyrø et al. 2013; Lacoppidan et al. 2015; Lassale et al. 2016; Lemming et al. 2018; Olsen et al. 2011). All studies used a food frequency questionnaire to assess dietary intakes, apart from one study that used 4-day food records (Tertsunen et al. 2020). Ten studies used a traditional 6-point scale (0–6) to define the ND score (Gunge et al. 2017; Hansen et al. 2017; Kyrø et al. 2013; Lacoppidan et al. 2015; Lassale et al. 2016; Lemming et al. 2018; Olsen et al. 2011; Roswall, Li, et al. 2015; Roswall, Sandin, Löf, et al. 2015; Roswall, Sandin, Scragg, et al. 2015), one study used a 18-point scale (0–18; Galbete et al. 2018), and other two studies a 25-point scale (0–25; Kanerva, Rissanen, et al. 2014; Tertsunen et al. 2020). The components of the ND score were whole-grain bread/or rye bread, root vegetables, cabbage/or cruciferous vegetables, oatmeal, apples and pears, and fish/selfish in the traditional 6-point scale, and were whole grain and rye bread, berries, fish, apples and pears, cabbage and cruciferous, root vegetables, low-fat dairy products, potatoes, and vegetable fats (excluding olive oil) in the 18-point scale. The 25-point scale also consisted of all fruits and berries, roots/pulses and vegetables, whole grains (rice, pasta), fat-free milk and milk (<2% fat), fish, ratio of polyunsaturated fatty acids to (saturated fatty acids + trans-fatty acids), processed and unprocessed meat (negative score), total fat as a percentage of total energy intake (negative score), and alcohol (negative score). All studies were at high quality on the basis of the Newcastle Ottawa Scale (Supporting Information Table S2).

All-cause mortality

Six prospective cohort studies (five publications) with 32,235 cases of all-cause mortality among 548,054 participants were included in the analysis (Lassale et al. 2016; Lemming et al. 2018; Olsen et al. 2011; Roswall, Sandin, Löf, et al. 2015; Tertsunen et al. 2020). All studies were from Europe and controlled for body mass index (BMI) and smoking status. Highest compared to the lowest category of adherence to the ND was associated with a 22% lower risk of all-cause mortality (RR: 0.78, 95%CI: 0.69, 0.87; $P < 0.001$, Figure 1 and Table 2), with moderate evidence of heterogeneity ($I^2 = 51\%$, $P_{\text{heterogeneity}} = 0.07$). The RR remained significant when each study was sequentially removed from the main analysis (RR range: 0.73 to 0.81; Supporting Information Table S3). In this sensitivity analysis, all of the observed heterogeneity was explained by the Swedish Mammography Cohort Study (Lemming et al. 2018) and when this study was excluded, the heterogeneity disappeared (RR: 0.73, 95%CI: 0.70, 0.76; $I^2 = 0\%$).

Four cohort studies were eligible for dose-response analysis (Lassale et al. 2016; Lemming et al. 2018; Roswall, Sandin, Löf, et al. 2015; Tertsunen et al. 2020). Each 2-unit increment in the ND score was associated with a 9% low risk (RR: 91, 95%CI: 90, 92; Table 2 and Supporting Information Figure S2). A nonlinear dose-response meta-analysis suggested an inverse linear association between adherence to the ND and the risk of all-cause mortality ($P_{\text{nonlinearity}} = 0.51$, $P_{\text{dose-response}} < 0.001$; $n = 4$; Figure 2A).

Table 2. The association between the Nordic diet score and the risk of chronic disease and mortality.

			Highest vs. lowest category meta-analysis			Dose-response meta-analysis (2-unit increase)		Certainty of evidence
Outcome	*n*	Participants/cases	RR (95%CI)	*P*-value	I^2, $P_{heterogeneity}$	RR (95%CI)	I^2, $P_{heterogeneity}$	Grade
All-cause mortality	6	548,054/32,235	0.78 (0.69, 0.87)	<0.001	51%, 0.07	0.91 (0.90, 0.92)	94%, <0.001	⊕⊕*oo*
CVD mortality	4	497,764/6636	0.78 (0.74, 0.83)	<0.001	70%, 0.02	0.89 (0.87, 0.92)	69%, 0.02	⊕⊕*oo*
Cancer mortality	4	497,764/11785	0.86 (0.80, 0.93)	<0.001	83%, 0.01	0.95 (0.93, 0.98)	67%, 0.03	⊕⊕*oo*
Type 2 diabetes	4	89,353/9283	0.90 (0.82, 0.99)	0.03	33%, 0.21	0.93 (0.90, 0.96)	40%, 0.17	⊕⊕*oo*
Stroke	3	126,196/3302	0.88 (0.79, 0.98)	0.02	3%, 0.36	0.95 (0.90, 0.99)	6%, 0.34	⊕⊕*oo*
Miocardial infarction	3	82,116/2634	0.80 (0.68, 0.95)	0.01	47%, 0.15	0.92 (0.88, 0.98)	65%, 0.09	⊕⊕*oo*
Colorectal cancer	3	101,102/1339	0.86 (0.80, 1.05)	0.30	54%, 0.12	0.96 (0.89, 1.03)	70%, 0.04	⊕*ooo*
Breast cancer	1	44,296/1464	1.08 (0.91, 1.27)	–	–	–	–	–

Abbreviations: CHD: coronary heart disease; CVD: cardiovascular disease; RR: relative risk.
$P < 0.05$ was considered as statistically significant.
[a]⊕*ooo*: very low; ⊕⊕*oo*: low; ⊕⊕⊕*o*: moderate; ⊕⊕⊕⊕: high.

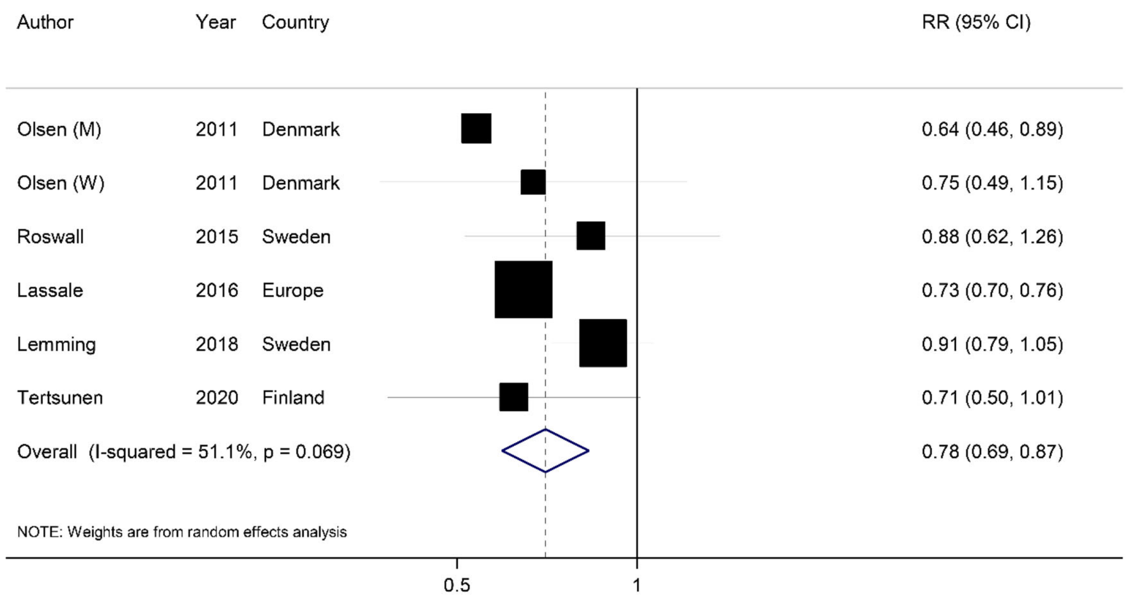

Figure 1. Relative risk of all-cause mortality for the highest compared to the lowest category of adherence to the Nordic diet. RR: relative risk; M: men; W: women.

Cardiovascular and cancer mortality

Four prospective cohort studies reported 6636 cases of CVD mortality and 11,785 cases of cancer mortality among 497,764 participants (Lassale et al. 2016; Lemming et al. 2018; Roswall, Sandin, Löf, et al. 2015; Tertsunen et al. 2020). All studies adjusted for BMI, age, and smoking status. The results showed that being in the highest versus lowest category of the ND score was associated with 22% lower risk of CVD mortality (RR: 0.78, 95%CI: 0.74, 0.83; $P < 0.001$, Figure 3 and Table 2), with high evidence of heterogeneity (($I^2 = 70\%$, $P_{heterogeneity} = 0.02$). The RR remained significant when each study was sequentially removed from the analysis (RR range: 0.75 to 0.84; Supporting Information Table S4). Step-by-step exclusion of each study showed that most of the heterogeneity in the data was explained by the EPIC study (Lassale et al. 2016) (RR: 0.84, 95%CI: 0.77, 0.92; $I^2 = 14\%$).

There was also a 14% lower risk of cancer mortality (RR: 0.86, 95%CI: 0.80, 0.93; $P < 0.001$, Figure 4 and Table 2) for the highest compared with the lowest category of the ND score. The evidence of heterogeneity was high ($I^2 = 83\%$, $P_{heterogeneity} = 0.001$). In the sensitivity analysis, the RR ranged from 0.79 (0.95%CI: 0.73, 0.86) after exclusion of the Swedish Mammography Cohort (Lemming et al. 2018) to 0.99 (95%CI: 0.89, 1.11) after exclusion of the EPIC study (Lassale et al. 2016) (Supporting Information Table S5). Sensitivity analysis also showed that all of the between-study heterogeneity was explained by the Swedish Mammography Cohort (RR: 0.79, 95%CI: 0.73, 0.86; $I^2 = 0\%$).

All included studies reported sufficient data for dose-response analysis. Each 2-unit increment in the ND score was associated with an 11% lower risk of CVD mortality (Supporting Information Figure S3 and Table 2) and a 5% lower risk of cancer mortality (Supporting Information Figure S4 and Table 2). A nonlinear dose-response meta-analysis suggested an inverse linear association between adherence to the ND and the risk of mortality due to CVD ($P_{nonlinearity} = 0.68$, $P_{dose\text{-}response} < 0.001$; $n = 4$; Figure 2B) and cancer ($P_{nonlinearity} = 0.98$, $P_{dose\text{-}response} = 0.01$; $n = 4$; Figure 2C).

Cardiovascular diseases incidence

In three cohort studies (two publications) with 82,116 participants, 2634 cases of myocardial infraction were diagnosed (Galbete et al. 2018; Gunge et al. 2017). All studies adjusted for BMI, age, smoking status, and physical activity. Greater adherence to the ND (highest vs. lowest category meta-analysis) was associated with a 20% lower risk of myocardial

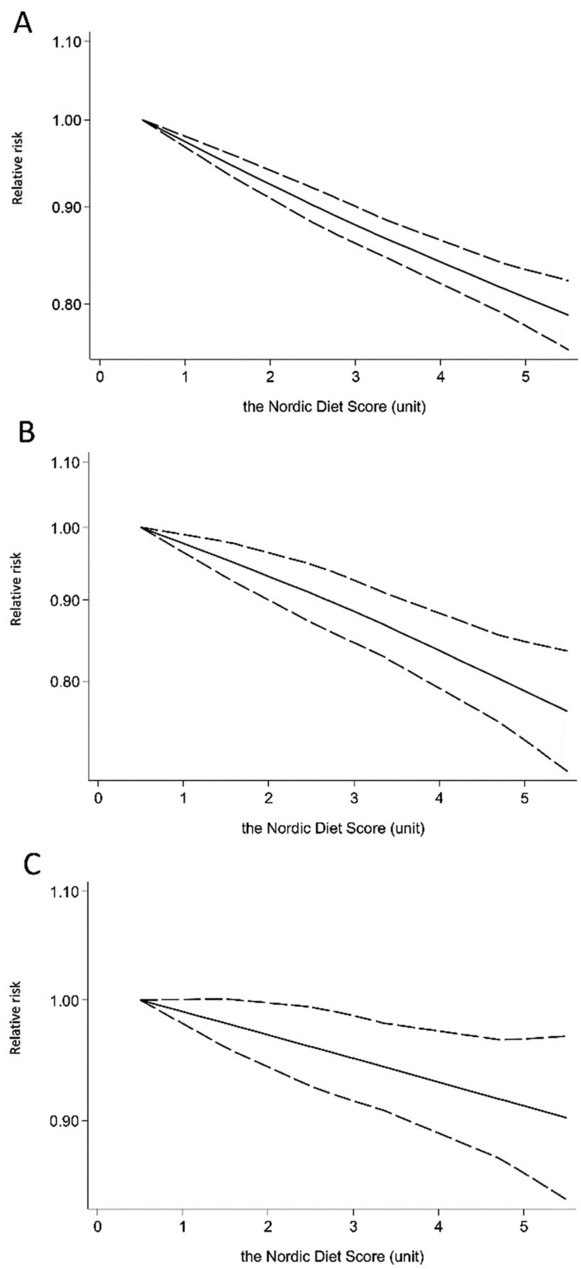

Figure 2. Dose-response association between adherence to the Nordic diet and the risk of (A) all-cause mortality; (B) cardiovascular mortality; (C) cancer mortality. Solid lines represent relative risk and dashed lines represent 95%CI.

infraction (RR: 0.80, 95%CI: 0.68, 0.95; $P = 0.01$, Supporting Information Figure S5), with moderate evidence of heterogeneity ($I^2 = 47\%$, $P_{heterogeneity} = 0.15$). Two studies (one publication) reported data for dose-response analysis (Gunge et al. 2017), and the results suggested an 8% lower risk of myocardial infarction for each 2-unit increase in the ND score (RR: 0.92, 95%CI: 0.88, 0.98; Supporting Information Figure S6 and Table 2).

The incidence of 3302 stroke cases was seen in three cohorts with 126,196 participants (Galbete et al. 2018; Hansen et al. 2017; Roswall, Sandin, Scragg, et al. 2015). In these studies, BMI, age, and smoking status were adjusted for. Highest compared to the lowest category of adherence to the ND was associated to a 12% lower risk of stroke (RR: 0.88, 95%CI: 0.79, 0.98; $P = 0.02$, Supporting Information Figure S7). The finding was accompanied by low evidence of heterogeneity ($I^2 = 3\%$, $P_{heterogeneity} = 0.36$).

All studies were eligible for dose-response analysis. Each 2-unit increment in the ND score was associated with a 5% lower risk (Supporting Information Figure S8 and Table 2). A dose-response meta-analysis showed an inverse linear association between adherence to the ND and the risk of incidence of stroke ($P_{nonlinearity} = 0.71$, $P_{dose\text{-}response} = 0.03$; $n = 3$; Supporting Information Figure S9).

Type 2 diabetes

The results of four prospective cohort studies (three publications) with 9283 cases of type 2 diabetes among 89,353 participants (Galbete et al. 2018; Kanerva, Rissanen, et al. 2014; Lacoppidan et al. 2015) showed that being in the highest compared to the lowest category of the ND score was significantly associated with a lower risk of type 2 diabetes (RR: 0.90, 95%CI: 0.82, 0.99; $P = 0.03$, Figure 5 and Table 2), with moderate evidence of heterogeneity ($I^2 = 33\%$, $P_{heterogeneity} = 0.21$). All studies controlled for BMI, age, and physical activity. The RR ranged from 0.85 (95%CI: 0.76, 0.95) when the EPIC-Potsdam study (Galbete et al. 2018) was removed, to 0.96 (0.86, 1.07) when the Danish diet, cancer and health cohort (men) (Lacoppidan et al. 2015) was removed (Supporting Information Table S6).

All studies were eligible for dose-response analysis. A 2-unit increment in the ND score was related to a 7% lower risk (RR: 0.93, 95%CI: 0.90, 0.96; Supporting Information Figure S10 and Table 2). There was an inverse monotonic association between adherence to the ND and the risk of incidence of type 2 diabetes ($P_{nonlinearity} = 0.17$, $P_{dose\text{-}response} = 0.05$; $n = 4$; Supporting Information Figure S11).

Colorectal cancer incidence

Three cohort studies (two publications) with 101,102 participants reported a number of 1339 cases of CRC during their follow-up durations (Kyrø et al. 2013; Roswall, Li, et al. 2015). The results showed that greater adherence to the ND (highest vs. lowest category) was not associated with the risk of CRC (RR: 0.86, 95%CI: 0.70, 1.05; $P = 0.30$, Supporting Information Figure S12 and Table 2), with moderate evidence of heterogeneity between studies ($I^2 = 53\%$, $P_{heterogeneity} = 0.12$). Dose-response analysis indicated no association between adherence to the ND with colorectal cancer risk (Supporting Information Figure S13 and Table 2).

Quality of the evidence

The certainty of the evidence was rated by the GRADE tool. The certainty in the estimates was rated low for all-cause, CVD, and cancer mortality, type 2 diabetes, stroke, and myocardial infarction, and very low for colorectal cancer (Supporting Information Table S7). The main reason for downgrading the evidence was serious indirectness since almost all studies included in the present review were

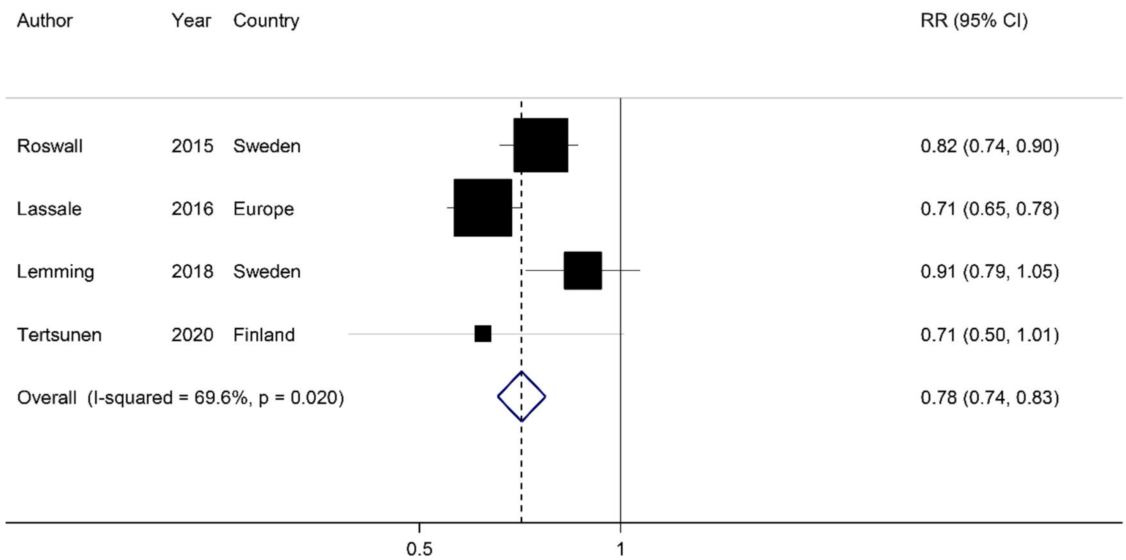

Figure 3. Relative risk of cardiovascular mortality for the highest compared to the lowest category of adherence to the Nordic diet. RR: relative risk.

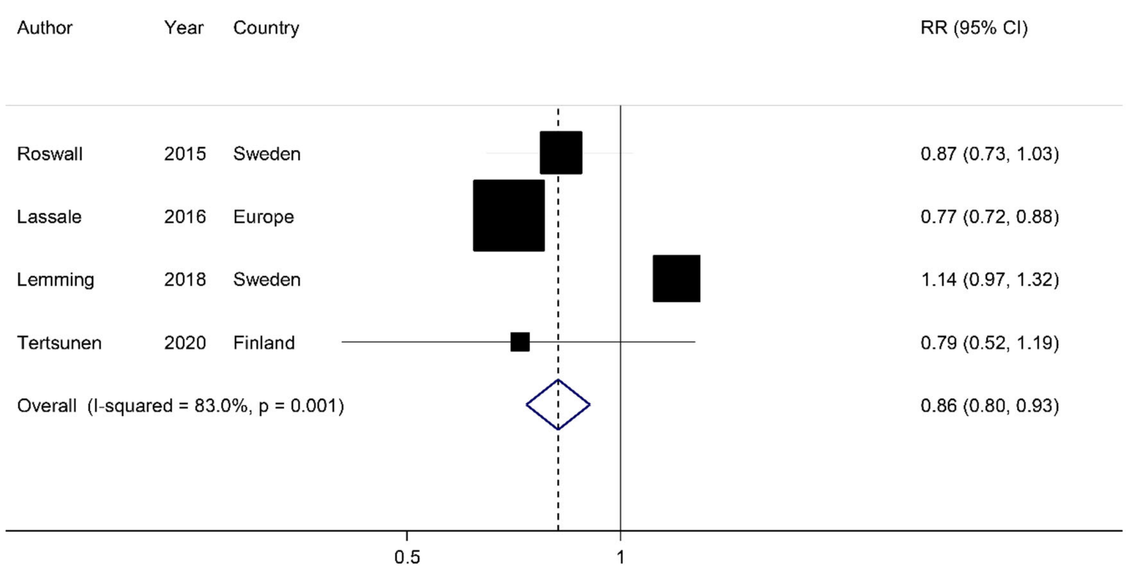

Figure 4. Relative risk of cancer mortality for the highest compared to the lowest category of adherence to the Nordic diet. RR: relative risk.

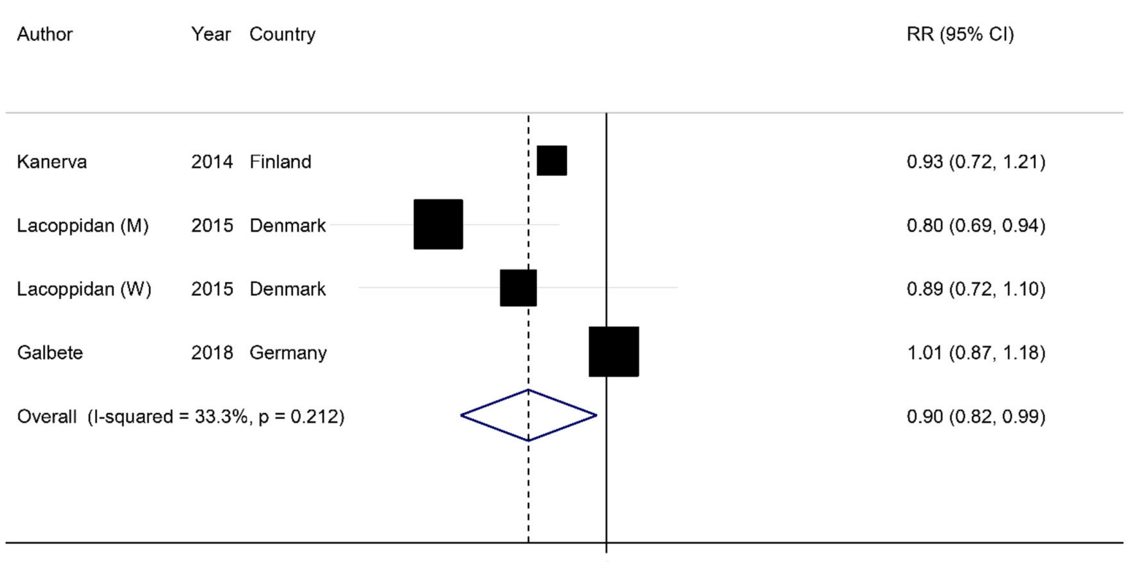

Figure 5. Relative risk of type 2 diabetes for the highest compared to the lowest category of adherence to the Nordic diet. RR: relative risk; M: men; W: women.

conducted in Northern European countries. The evidence was also downgraded for imprecision for colorectal cancer.

Discussion

This systematic review and meta-analysis was performed on 13 prospective cohort studies with 50,471 deaths and non-communicable chronic diseases among 930,153 participants. The results showed that greater adherence to this healthy dietary pattern was associated with a 22% lower risk of all-cause mortality. An inverse linear association was found for the association between the ND and mortality due to all-cause, CVD, and cancer. With regard to cause-specific mortality, greater adherence to the ND was associated with a lower risk of CVD and cancer mortality by 22% and 14%, respectively. We also found an inverse linear association between adherence to the ND and the risk of CVD and cancer mortality. Moreover, greater adherence to the ND was associated with a lower risk of myocardial infraction (by 20%), stroke (by 12%), and type 2 diabetes (by 10%) that were confirmed by inverse monotonic associations in dose-response meta-analyses.

In accordance with our findings, previous meta-analyses on RCTs showed beneficial effects of the ND on cardiometabolic risk factors such as high blood pressure (Ndanuko et al. 2016; Ramezani-Jolfaie, Mohammadi, and Salehi-Abargouei 2019), and high low-density lipoprotein cholesterol (Ramezani-Jolfaie, Mohammadi, and Salehi-Abargouei 2019). A systematic review and meta-analysis of observational studies found an inverse association between adherence to the ND and levels of C-reactive protein (Kanerva, Kaartinen, Rissanen, et al. 2014). Our results regarding the inverse association of the ND with disease risks are consistent with those of other plant-based healthy dietary patterns such as Dietary Approaches to Stop Hypertension (DASH) dietary pattern (Milajerdi et al. 2018; Salehi-Abargouei et al. 2013), Healthy Eating Index and Alternative Healthy Eating Index (Milajerdi et al. 2018), and the Mediterranean dietary pattern (Rosato et al. 2019; Sofi et al. 2014; Soltani et al. 2019).

Overall, our results indicated that higher adherence to the ND might be helpful in the prevention of chronic diseases such as CVD and type 2 diabetes. This dietary pattern mainly focuses on high consumption of fruits, vegetables, whole grains, fish, rapeseed oil, and low-fat dairy products; as well as low consumption of processed meat and alcohol (Kanerva, Kaartinen, Schwab, et al. 2014). The results of the previous research showed that increased consumption of healthy components of the ND such as whole grains, fish, and vegetables was associated with a lower risk of all-cause mortality (Schwingshackl et al. 2017). Increased consumption of fruits, dietary fibers, vegetables, nuts and lower consumption of sodium following higher adherence to the ND could be helpful in decreasing blood pressure, a major risk factor for CVD (Adler et al. 2014; Hu and Willett 2002). Besides, it seems that high consumption of rapeseed oil, a rich source of alpha-linolenic acid, could be beneficial in the management of CVD risk factors such as dyslipidemia and high blood pressure (Baxheinrich et al. 2012; Pedersen et al. 2000). Additionally, this pattern is characterized by high consumption of berries, as rich dietary source of polyphenols, that might have strong antioxidant and anti-inflammatory properties (Basu, Rhone, and Lyons 2010; Lopez-Garcia et al. 2004). Finally, the ND encourages high consumption of fish (rich source of polyunsaturated fatty acids) that has been shown to be associated with a lower risk of all-cause and CVD mortality (Jayedi, Shab-Bidar, et al. 2018).

The ND has some similarities with other plant-based dietary patterns such as the Mediterranean and DASH dietary patterns. All these healthy patterns recommend higher consumption of fruit, vegetables, whole grains, and fish. A large prospective cohort study in 10 European countries assessed the association of 11 different dietary quality index with the risk of all-cause, CVD, and cancer mortality, which showed that higher adherence to healthy dietary patterns such as the Mediterranean, DASH, and the Nordic dietary patterns was associated with a lower risk of mortality to a relatively same degree (Lassale et al. 2016). Another prospective cohort study showed that higher adherence to the Mediterranean and the Nordic dietary pasterns were associated with a lower risk of all-cause and CVD mortality. However, further analysis showed that the higher adherence to the ND was no longer associated with mortality risk after additional adjustment for the Mediterranean diet score (Lemming et al. 2018). The Swedish Women's Lifestyle and Health cohort study showed that higher adherence to the Mediterranean and the Nordic dietary patterns were associated with a 6% and a 13% lower risk of all-cause mortality, respectively (Lagiou et al. 2006; Roswall, Sandin, Löf, et al. 2015). These findings suggest that application of the ND alongside with the other healthy eating patterns such as DASH and the Mediterranean diets can be an effective approach in the prevention of chronic diseases. However, further prospective observational studies are needed to confirm these results, especially in different geographical regions with different dietary habits and genetic susceptibilities.

This study has some strengths. First, for the first time, we studied the association of the ND score, a new-developed healthy dietary quality index, with the risk mortality and morbidity based on the results of the 13 prospective cohort studies. Previous epidemiologic studies have shown inverse associations between higher adherence to healthy dietary patterns such as DASH and the Mediterranean dietary patterns with disease risks. However, regarding the ND, there was no sufficient available evidence. We included 13 high-quality prospective cohort studies with relatively long-term follow-up durations and large numbers of participants. Second, we assessed the dose-response relationships between adherences to the ND and all-cause and cause-specific mortality, which showed that the risk of mortality decreased linearly along with the increase in adherence to the ND.

This study also has some limitations. Most importantly, there were low numbers of studies for most outcomes and thus, more research is needed to confirm the present results. Second, all included studies were from European countries, Especially Northern European countries, which limited the generalizability of the findings. Third, although the analyses were performed with too few studies, the evidence of heterogeneity was moderate for all-cause mortality, myocardial infarction and type 2 diabetes, and high for CVD- and cancer mortality. However, in all analyses, almost all included studies reported effect sizes below one and thus, the observed heterogeneity was largely due to differences in the magnitude of the effect sizes, and not due to differences in the direction of the associations. Finally, we had too few studies to test the publication bias and thus, the results may have been overestimated due to potential for publication bias.

Conclusions

In conclusion, the results of this meta-analysis showed that greater adherence to the ND may be associated with a lower risk of all-cause, CVD and cancer mortality, as well as lower risks of stroke, myocardial infarction, and type 2 diabetes. Higher adherence to the ND was not associated with the risk of CRC. These results highlight the vital roles of adherence to healthy dietary patterns in relation to the prevention of chronic disease.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Author contributions

Y.JP. contributed to the acquisition of data for the work and drafted the manuscript. A.J. contributed to the conception, design of the work, analysis, and interpretation of the data. K.DJ. critically revised the manuscript. S.S-B. contributed to the interpretation of the data and critically revised the manuscript. All authors read and approved the integrity and accuracy of the manuscript.

ORCID

Ahmad Jayedi http://orcid.org/0000-0003-4231-3147

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