Association Between Dietary Habits in Midlife With Dementia Incidence Over a 20-Year Period

Author(s):
Isabelle Glans, MD; Emily Sonestedt, PhD; Katarina Nägga, MD; PhD; Anna-Märta Gustavsson, MD, PhD; Estére González-Padilla, MD; Yan Borne, PhD; Erik Stomrud, MD, PhD; Olle Melander, MD, PhD; Peter Nilsson, MD, PhD; Sebastian Palmqvist, MD, PhD; Oskar Hansson, MD, PhD

Corresponding Author:
Isabelle Glans, isabelle.glans@med.lu.se

Affiliation Information for All Authors: 1. Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Sweden; 2. Memory Clinic, Skåne University Hospital, Malmö, Sweden; 3. Nutritional Epidemiology, Department of Clinical Sciences in Malmö, Lund University, Skåne University Hospital, Malmö, Sweden; 4. Department of Acute Internal Medicine and Geriatrics, Linköping University, Linköping, Sweden; 5. Department of Clinical Sciences Malmö, Lund University, Skåne University Hospital, Malmö, Sweden

Equal Author Contribution:
SP and OH contributing equally as senior authors.

This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Contributions:
Isabelle Glans: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Emily Sonestedt: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Katarina Nägga: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Anna-Märta Gustavsson: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Esther González-Padilla: Drafting/revision of the manuscript for content, including medical writing for content
Yan Borne: Drafting/revision of the manuscript for content, including medical writing for content
Erik Stomrud: Drafting/revision of the manuscript for content, including medical writing for content
Olle Melander: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Peter Nilsson: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Sebastian Palmqvist: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Oskar Hansson: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Figure Count:
1

Table Count:
3

Search Terms:

Acknowledgment:
The authors wish to thank Per Wändell, senior professor in General Medicine at the Department of Neurobiology, Care Sciences and Society, at Karolinska Institutet (KI), for the discussion initiating the present study. The authors also thank participants and research staff of the MDCS.

Study Funding:
Work at the authors’ research center was supported by the Swedish Research Council (2016-00906, #2018-02052), the Knut and Alice Wallenberg foundation (2017-0383), the Marianne and Marcus Wallenberg foundation (2015.0125), the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson’s disease) at Lund University, the Swedish Alzheimer Foundation (AF-939932, #AF-940046), the Swedish Brain Foundation (FO2021-0293, #FO2020-0271), The Parkinson foundation of Sweden (1280/20), the Konung Gustaf V:s och Drottning Victorias Frimurarstiftelse, the Skåne University Hospital Foundation (#2020-000028), Regionalt Forskningsstöd (2020-0314, Projekt-2020-0383) and the Swedish federal government under the ALF agreement (2018-Projekt0279, #2018-Projekt0226).

Disclosures:
S. Palmqvist has served on scientific advisory boards and/or given lectures in symposia sponsored by F. Hoffmann-La Roche, Biogen, and Geras Solutions. O. Hansson has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from Roche, Genentech, Siemens, Biogen, Alzpath, and Cerveau. I. Glans reports no disclosures relevant to the manuscript. E. Sonestedt reports no disclosures relevant to the manuscript. K. Nägga reports no disclosures relevant to the manuscript. A-M. Gustavsson reports no disclosures relevant to the manuscript. E. González-Padilla reports no disclosures relevant to the manuscript. Y. Borne reports no disclosures relevant to the manuscript. E. Stomrud reports no disclosures relevant to the manuscript. O. Melander reports no disclosures relevant to the manuscript. P. M. Nilsson reports no disclosures relevant to the manuscript.
Background and Objectives: Dementia cases are expected to triple during the next 30 years, highlighting the importance of finding modifiable risk factors for dementia. The aim of this study is to investigate whether adherence to conventional dietary recommendations or to a modified Mediterranean diet are associated with subsequent lower risk of developing all-cause dementia, Alzheimer’s disease (AD), vascular dementia (VaD), or with future accumulation of AD-related β-amyloid (Aβ) pathology.

Methods: Baseline examination in the prospective Swedish population-based Malmö Diet and Cancer Study (MDCS) took place in 1991-1996 with a follow-up for incident dementia until 2014. Non-demented individuals born 1923-1950 and living in Malmö were invited to participate. 30,446 were recruited (41% of all eligible). 28,025 had dietary data and were included in the present study. Dietary habits were assessed with a 7-day food diary, detailed food frequency questionnaire and one-hour interview. Main outcomes were incident all-cause dementia, AD or vascular dementia determined by memory clinic physicians. Secondary outcome was Aβ-accumulation measured using cerebrospinal fluid (CSF) Aβ42 (n=738). Cox proportional hazard models were used to examine associations between diet and risk of developing dementia (adjusted for demographics, co-morbidities, smoking, physical activity, and alcohol).

Results: 61% were women and the mean (SD) age was 58.1 (7.6) years). 1,943 (6.9%) were diagnosed with dementia (median follow-up, 19.8 years). Individuals adhering to conventional dietary recommendations did not have lower risk of developing all-cause dementia (hazard ratio [HR] comparing worst with best adherence, 0.93, 95%CI 0.81-1.08), AD (HR 1.03, 0.85-1.23) or VaD (HR 0.93, 0.69-1.26). Neither did adherence to the modified Mediterranean diet lower the risk of developing all-cause dementia (HR 0.93 0.75-1.15), AD (HR 0.90, 0.68-1.19) or VaD (HR 1.00, 0.65-1.55). The results were similar when excluding participants developing dementia within 5 years or those with diabetes. No significant associations were found between diet and abnormal Aβ accumulation conventional recommendations: OR 1.28 (0.74-2.24) and modified Mediterranean diet: 0.85 (0.39-1.84).

Discussion: In this 20-year follow-up study, neither adherence to conventional dietary recommendations nor to modified Mediterranean diet were significantly associated with subsequent reduced risk for developing all-cause dementia, AD dementia, VaD or AD-pathology.
Introduction
The estimated number of dementia cases was globally 47 million in 2015 and is expected to triple during the next 30 years.\textsuperscript{1} Since effective treatment is lacking, effectively targeting modifiable risk factors for cognitive impairment and dementia could provide great benefits for this population and reduce societal costs. In addition to a large burden for patients and relatives, there is a tremendous burden for the health care-system, with a global cost of US$1 trillion annually.\textsuperscript{2} As acknowledged by the 2020 report of the Lancet Commission on Dementia prevention, intervention, and care, modifiable risk factors account for 40\% of worldwide dementia cases.\textsuperscript{2}

A modifiable and controversial risk factor for cognitive impairment and dementia is dietary habits. Several studies have examined how dietary habits affect incidence in dementia disorders, with inconsistent results. Systematic reviews and meta-analyses conclude that adhering to Mediterranean diet may contribute to a slowing of cognitive decline and a lower incidence in dementia.\textsuperscript{3-5} However, there are several important methodological weaknesses in many of the previous studies including: 1) exclusively relying on data from retrospective food frequency questionnaires with possible report biases, 2) insufficient follow-up time, 3) inclusion of participants older than 70 years, with a possible cognitive impairment already affecting diet (i.e., reversed causality), and 4) usage of all-cause dementia as outcome, missing the possibility of diet being differently associated with specific dementia diseases, such as Alzheimer’s disease (AD) which is the most common accounting for 60-70\% of all dementia cases, and the second most common caused by cerebrovascular disease vascular dementia (VaD), which exhibit different genetic and lifestyle risk factor patterns.

In order to further understand the mechanisms between a potential dietary influence on the incidence of specific dementia disorders, it would be an advantage to examine the association between diet and the underlying disease pathology. Accumulation of amyloid-\(\beta\) (A\(\beta\)) in the brain is the cause of AD and it can be detected using cerebrospinal fluid (CSF) analysis of
Aβ42 or Aβ PET imaging. However, large-scale longitudinal studies evaluating potential associations between mid-life diet and amyloid pathology are lacking.

In the present observational study, we prospectively collected detailed dietary data in mid-life from a large population-based study of more than 28,000 individuals. The aim was to examine the association between adherence to general dietary guidelines as well as Mediterranean diet of dementia incidence. Development of any kind of dementia during 20 years was used as primary outcome. Secondary outcomes were development to specifically AD dementia or VaD, respectively. In a convenience subsample (n=738), we performed an exploratory analysis studying the association between dietary components and future accumulation of AD-related pathology measured using CSF analysis of Aβ42.

Methods

Study Population

Data were obtained from the Malmö Diet and Cancer study (MDCS), which is a population based prospective cohort study from the city of Malmö, Sweden. Between 1991 and 1996, men born in 1923-1945 and women born 1923-1950 living in Malmö were deemed eligible and invited to participate. Exclusion criteria were language problems and mental incapacity, which could preclude participants from fulfilling the questionnaires properly. In all, 30,446 individuals attended at least a part of the baseline examination which included a self-administrated questionnaire which assessed education, occupation, physical activity, social network, use of tobacco and alcohol, current health, medical history, current medication, and family history of disease in close relatives, along with body composition measurements and dietary assessments. Participation reached 40.8% of the eligible population.

A subpopulation of the study participants underwent lumbar puncture with analyses of CSF Aβ42 when referred to the Memory clinic at Skåne University Hospital, Malmö, after
developing clinical signs of cognitive impairment. This represents a convenience subsample of the MDCS and should not be regarded as a representative subsample of the whole study.

**Dietary Assessments and Method**

Information on dietary habits was obtained from all participants at baseline through 1) a diet diary and 2) a self-administered food frequency questionnaire (FFQ), which provided complementary information, and 3) a 45-60 min interview with trained personnel. Detailed information on the dietary data collection procedure, including administration of the FFQ and diary, was given at the first visit by trained research nurses. In the 7-day food diary, participants recorded cooked meals, cold beverages, drugs, natural remedies, and dietary supplements. In the 168-item FFQ participants stated, with reference period last year, regularly consumed foods not covered by the food diary (i.e. breakfast and snacks), portion size (based on pictures of four portions sizes for 48 food items) and frequency of food consumed. In addition, participants underwent a 1 hour-interview with trained personnel collecting additional information on cooking methods, food choices and portion sizes, and to make sure the information from the diary and FFQ was correct. Halfway through the baseline data collection (in 1994), the interview routines changed to reduce interview time to 45 minutes. Average daily food intake (g/day) was calculated by combining the data from the food diary and the FFQ. Energy and nutrient intakes were calculated by combining the data on average food intake with the MDCS database originating from the Swedish National Food agency database. The combined dietary method used in MDCS has been validated against 18-days of weighted food records with correlation coefficients for men/women of 0.60/0.74 for sugar, 0.74/0.69 for fibre, 0.65/0.58 for vegetables, 0.60/0.77 for fruits, 0.35/0.65 for fish, 0.82/0.91 for meat, and 0.50/0.65 for wine.

**Swedish Dietary Guidelines Score and modified Mediterranean Diet Score**
A Swedish dietary guidelines score (SDGS), designed to portray a healthy dietary pattern, based on Swedish nutrition recommendations and dietary guidelines\textsuperscript{10}, which are in line with dietary recommendations in the U.S.\textsuperscript{11} and UK\textsuperscript{12}, was calculated for each participant based on average daily food intake. The SDGS is based on consumption of five dietary domains: Dietary fibre $\geq 2.4$ g/MJ from non-alcohol energy; added sugar $\leq 10\%$ of non-alcohol energy; fish and shellfish $\geq 300$g/week; fruit and vegetables $\geq 400$g/day; and red and processed meat $\leq 500$g/week. Reaching recommendations yielded 1 point /domain, with a maximum SDGS of 5 points. A similar index has previously been developed within MDCS.\textsuperscript{13} In the modified index, we included added sugar (instead of sucrose) and red and processed meat (instead of saturated and polyunsaturated fat). Based on the SDGS participants were divided into the following groups: low adherence (0-1 points), moderate adherence (2-3 points) and high adherence (4-5 points).

A modified Mediterranean diet score (mMDS) was created based on the original 14-item score used for the Prevención con Dieta Mediterránea (PREDIMED) study.\textsuperscript{14} The mMDS consists of 10 dietary domains: 1) Vegetable oils ($\geq 54$ g/day), 2) Vegetables including legumes ($\geq 300$ g/day), 3) Fruits ($\geq 300$ g/day), 4) Red and processed meat (<125 g/day), 5) Butter, margarine, cream (<12g/day), 6) Soda (<200 g/day), 7) Wine ($\geq 100$ g/day), 8) Fish and seafood ($\geq 53.6$ g/day or $\geq 85.7$ g/day, respectively), 9) Pastries and candy (<21.4 g/day or <12.8 g/day, respectively) and 10) Nuts and seeds ($\geq 12.8$ g/day). Reaching recommendations yielded 1 point/domain with a maximum mMDS of 10 points (meets all recommendations). Domain “legumes” was incorporated in the vegetable-domain. In addition, “sofrito”, a typical Mediterranean sauce, was excluded in the mMDS, due to low consumption in Nordic countries and the lack of information from the food records. Two domains were further excluded from the index (olive oil as main culinary lipid, and poultry more than red meats) due to lack of questions referring to this in the present FFQ.\textsuperscript{14} However, the consumption of
olive oil was added to the intake of other vegetable oils because the consumption of these oils is usually low in the Nordic population. Based on the mMDS participants were divided into the following groups: low adherence (0-1 points), moderate adherence (2-4 points), high adherence (5-10 points). The regrouping was performed in order to have enough discrepancies between groups regarding dietary habits, and to avoid too small groups. (Supplementary eTable 1).

A Mediterranean Diet Score according to Panagiotakos et al.\textsuperscript{15} was calculated scoring 0-50 (poor to good adherence to Mediterranean diet recommendations). The original score is from 0-55 but here the domain “legumes” was incorporated in the domain “vegetables” due to low consumption in Nordic population. As in the case of mMDS, all vegetable oils were considered rather than olive oil alone. (Supplementary eTable 2).

\textit{Covariates}

Sociodemographic factors included age, sex and education. At baseline, participants completed a questionnaire including life-style factors and health status. Education level was divided into three subgroups as per study design: primary/elementary school (\leq 8 years), secondary school/high school (9-12 years) or higher education/university ($\geq$ 13 years), based on information from the questionnaire. From the questionnaire smoking status was divided into three groups (smokers, former smokers and never smokers), and physical activity as metabolic equivalent hours/week (MET/h/week). One MET is defined as the metabolic intensity when a person is at rest. MET/h/week was computed by multiplying time (hours) spent on each activity by the respective metabolic equivalent task (intensity) factor (MET).\textsuperscript{2} Information on alcohol consumption was derived both from the questionnaire and the 7-day record. Zero-consumers had reported no consumption during the past year. The other participants were stratified in quintiles separately in men and women (because of alcohol consumption and daily recommendations differ between men and women), with the following
spans: 0-3.4, 3.4-9.1, 15.7, 25.7 g/day (men) and 0-0.9, 4.3, 8.1, 14.0 g/day (women). APOE-
ɛ4 interaction analysis was performed to investigate a potentiating effect of this well-
established genetic risk factor for AD. Due to possible seasonal variations in dietary intake,
and that dietary interview was shortened in 1994, season and diet assessment method were
included in the analyses.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants received information about the study and gave written consent to participate.
Ethical approval was given by the Ethical Committee of Lund University, Lund, Sweden (LU
90-51).

Outcomes

The primary outcome was progression to all-cause dementia disorders. The secondary
outcomes were progression to AD dementia and VaD. The exploratory outcome was
abnormal Aβ status measured as increased levels of CSF Aβ42 (see Exploratory outcome CSF
Aβ42 below).

The primary and secondary diagnostic outcomes were based on registered
dementia diagnoses from the Swedish National Patient Register (NPR) throughout 2014. The
NPR covers both the Swedish Inpatient Register and the hospital-based outpatient register.
Diagnoses included AD dementia (ICD-10 and ICD-9 codes F00, G30, 331A/331.0), VaD
(F01, 290E/290.4), Parkinson disease dementia (F023), dementia with Lewy bodies (F028,
G318A), frontotemporal dementia (F020, G310, 331B/331.1), or unspecified dementia (F03,
290, 294B/294.1, 331C/331.2). After the register data delivery, trained physicians with
special interest in dementias, but not yet board-certified specialists, at the Memory Clinic at
Skåne University Hospital reviewed and validated all registered dementia diagnoses based on
symptoms, results of cognitive tests, brain imaging (computed tomography or magnetic resonance imaging reviewed by radiologists), and CSF concentrations of Aβ42 and tau phosphorylated at Thr181 (p-tau; when available) in accordance with the specific major neurocognitive disorders in DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). In uncertain cases two specialists in Neurology and Geriatrics, (OH and KN), respectively, with more than 10 years of experience in the field of dementia were involved. In cases where CSF was available, AD-diagnosis was based on the NIA-AA-criteria. Of the 1,943 cases with dementia, 1,507 (77.6%) were diagnosed at a specialized Memory Clinic.

The secondary outcomes were defined as pure AD, mixed AD and vascular pathology and VaD. Information from neuroimaging was used to validate VaD, and to differentiate between pure AD and AD with cerebrovascular disease (mixed AD and vascular pathology). Presence of significant cerebrovascular disease on neuroimaging led to a mixed AD diagnosis if AD was considered the primary cause.

**Exploratory outcome - CSF Aβ42**

CSF data was available for participants with signs of cognitive decline who had been referred to the Memory Clinic at Skåne University Hospital for further investigation. With lumbar puncture, CSF was collected between 1995 and 2015 according to a structured protocol. CSF concentrations of Aβ42 were measured using INNOTEST ELISA (Fujirebio Europe, Ghent, Belgium).

Cut-off values for CSF Aβ42 were established using mixture modelling. Because of a slight, assay-dependent drift in levels of CSF Aβ42 during the collection period 1995-2015, two different cut-offs were established for the period 1995-2003 (Aβ42 <484.8
pg/mL) and 2004-2015 (Aβ42 <577.1 pg/mL). This drift in INNOTEST CSF Aβ42 values during this time period is well known.20

Statistical Analyses
Demographic data are presented as means (standard deviations, SD) or numbers (n) and percent (%). Cox proportional hazard models, with years between baseline and event as time variable, were used to examine associations between SDGS and mMDS and risk of developing dementia. Event was defined as all-cause dementia (primary outcome) or specific dementia disorder (secondary outcome). Censoring occurred at the recorded date of dementia, time of death or at time of register data delivery (31/12/2014). By using this approach, the competing risk of death was assessed by estimating cause-specific HR for dementia, in accordance with recommendations when the study objective is etiological.24 All analyses were adjusted for age, sex, education, season, dietary sampling method and total energy intake (kJ) in Model 1. In Model 2, the following lifestyle variables were also included: smoking (current, former, never), alcohol consumption (sex-specific quintiles), body mass index (BMI), and physical activity (METH/week). In Model 2, a total of 243 cases had missing data in any of these lifestyle variables and were thus excluded. Logistic regression analysis was used to examine the association between SDGS and Aβ42 accumulation, using CSF Aβ42 status as outcome.

In sensitivity analyses, participants diagnosed with dementia <5 years from baseline were excluded, to reduce the possible bias of cognitive impairment affecting dietary intake25 (i.e. a preclinical or prodromal dementia disorder). A total of 73 were excluded in this analysis. In another sensitivity analysis, participants with prevalent and incident diabetes mellitus were excluded to investigate the dietary association without being influenced by diabetes and the dietary restrictions that may accompany that disease.26 A total of 5,221
participants with diabetes were excluded, of which 405 developed dementia. Sensitivity analysis were also performed excluding participants that had made substantial changes in their dietary habits at any time before the baseline examination. In addition, another sensitivity analysis was performed only including individuals diagnosed at the Memory Clinic. Using the Mediterranean Diet Score according to Panagiotakos et al.\textsuperscript{15} was used in another sensitivity analysis.

All statistical analyses were performed using R (version 3.6.3). A p-value $<$0.05 was considered significant.

Data Availability Statement
The data that support the findings of this study are available from the Malmö Population-Based Cohorts Joint Database but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Malmö Population-Based Cohorts Joint Database.

Results
Baseline Characteristics
Individuals who underwent dietary assessments were included (n=28,098) in the present study. Participants with incomplete data on education (n=71) and where time to event was zero, meaning present dementia, (n=2) were excluded, resulting in a complete dataset of 28,025 individuals, which was used for the main analysis. See Figure 1 for an enrollment flow-chart. Of the 28,025 dementia-free participants at study recruitment in 1991-1994, a total of 1,943 (6.9\%) were diagnosed with dementia during a median of 19.8 (inter-quartile range [IQR] 4.8) years of follow-up. Comparison of baseline characteristics between complete
dataset and excluded group is shown in Supplementary eTable 3. Table 1 presents characteristics of participants who subsequently developed any type of dementia (all-cause dementia) compared with those who did not develop dementia. The individuals who subsequently developed dementia were significantly older at baseline and had a lower level of the education. There was no difference in sex, 61% were women in both groups. Neither SDGS nor mMDS differed between groups. Median time from baseline to any dementia diagnosis was 15.5 (IQR 6.7) years. Baseline characteristics across dietary adherence levels are shown in Supplementary eTable 4-5.

**Association between Diet and Risk of Developing All-Cause Dementia**

Associations between SDGS and development of all-cause dementia, AD dementia and VaD are presented in Table 2. Individuals who adhered to the dietary recommendations did not show a significantly lower risk of developing all cause dementia in Model 1 (HR 0.98, 95% CI: 0.95-1.02) or Model 2 (HR 0.99, 95% CI: 0.95-1.03) using SDGS as a continuous variable (0 to 5, poor to good adherence). Further, individuals adhering to dietary recommendations (SDGS 4-5) did not have lower risk of developing dementia in either Model 1 (HR=0.93; 95% CI: 0.81-1.08) nor in Model 2 (HR 0.95; 95% CI: 0.82-1.10) compared to those with low (SDGS 0-1), Table 2.

Neither did adherence to the modified Mediterranean diet lower the risk of developing all-cause dementia in Model 1 (HR 0.93, 95% CI: 0.75-1.15) or Model 2 (HR 1.00, 95% CI: 0.96-1.04) when using mMDS as a continuous variable. Individuals adhering to the modified Mediterranean diet (mMDS 5-10) did not have lower risk of developing all-cause dementia (HR 0.93, 95% CI 0.75-1.15) in Model 1 and (HR 0.95 95% CI: 0.76-1.18) in Model 2 (Table 3).

**Association between Diet and Risk of Developing Alzheimer’s disease or Vascular Dementia**
As shown in Table 2, no significant associations between SDGS as continuous variable and development of AD dementia (HR 0.99, 95% CI: 0.95-1.04) or VaD (HR 0.98, 95% CI: 0.91-1.06) were found. Individuals adhering to dietary recommendations (SDGS 4-5) did not have lower risk of developing AD dementia (HR 1.03, 95% CI: 0.85-1.23) or VaD (HR 0.93, 95% CI: 0.69-1.26) compared to those with low SDGS (0-1), AD dementia (HR 0.90, 95% CI: 0.68-1.19) or VaD (HR 1.00, 95% CI: 0.65-1.55) (Table 2).

Neither did adherence to modified Mediterranean diet lower the risk of developing AD dementia (HR 0.99 95% CI: 0.94-1.05) or VaD (HR 1.04 95% CI: 0.96-1.12) when analysing mMDS as a continuous variable. Individuals with the highest adherence to the modified Mediterranean diet (mMDS 5-10) did not have lower risk of developing AD dementia (HR 0.90 95% CI: 0.68-1.19) or VaD (HR 1.00 95% CI: 0.65-1.55) (Table 3).

Adjusted Kaplan-Meier curves displaying no effects of diet quality and incidence in all-cause dementia, ADD or VaD are shown in Supplementary eFigure 1.

**Sensitivity Analyses**

In sensitivity analyses, we excluded participants with incident dementia diagnosis within five years after baseline as well as participants with prevalent or incident diabetes, respectively. As for the main results no significant effect of lowering the risk of dementia were found between SDGS or the mMDS with development of all cause dementia, AD dementia or VaD (Supplementary eTable 6-9).

Further, in sensitivity analyses excluding participants indicating a substantial change in their dietary habits before baseline, no significant effect of lowering the risk of dementia were found between SDGS or the mMDS with development of all cause dementia, AD dementia or VaD (Supplementary eTable 10-11).
In sensitivity analysis using the Mediterranean Diet Score according to Panagiotakos et al.\textsuperscript{15} no significant effect of lowering the risk of all cause dementia, AD dementia or VaD were found (Supplementary eTable 12).

Further, there were no significant interaction effects between SDGS or the mMDS and the AD risk genotype \textit{APOE} \textit{ɛ}4 (Supplementary eTable 13-14).

Excluding participants not diagnosed at a Memory Clinic did not change the results (data not shown).

\textit{Diet and Deposition of CSF β-Amyloid}

A total of 777 subjects underwent lumbar puncture. Participants with missing CSF Aβ42 data were excluded (n=39), resulting in sample of 738 participants with available CSF Aβ42 data. Median time from baseline to CSF collection was 12.9 (IQR 7.4) years. Associations between SDGS and CSF Aβ42 status (normal/abnormal) are shown in the Supplementary eTable 15. No significant association between SDGS and CSF Aβ42 at follow-up was found. Individuals with the highest adherence to dietary recommendations (SDGS 4-5) did not have lower risk of having abnormal Aβ42 in CSF (OR 1.10, 95% CI: 0.66-1.84).

Associations between mMDS and CSF Aβ42 status (normal/abnormal) are shown in Supplementary eTable 16. No significant associations between mMDS and CSF Aβ42 at follow-up was found. Individuals with the highest adherence to the modified Mediterranean diet (mMDS 5-10) did not have lower risk of having abnormal Aβ42 in CSF (OR 0.82, 95% CI: 0.37-1.79; \( p = 0.69 \)). Additionally adjusting for time between baseline and CSF collection did not change the results. Neither, no significant association between Mediterranean Diet Score according to Panagiotakos et al.\textsuperscript{15} and abnormal Aβ42 in CSF (Supplementary eTable 17).
Discussion

Midlife self-reported diet quality according to dietary recommendations or according to the modified Mediterranean diet were not associated with subsequent reduced risk of developing all-cause dementia, AD dementia, or VaD over a median follow-up time of 19.8 years in this population-based prospective cohort study of 28,025 individuals. Further, diet was not associated with presence of Aβ pathology at follow-up.

The main strengths of the present study was the prospective study design, the large sample size, the long follow-up time of almost 20 years and the dietary assessment method of high quality, where food frequency questionnaire was complemented by interviews which improves the validity of the dietary data. In addition, the dementia diagnoses were validated by trained physicians at a Memory Clinic and are not merely register-based as in several previous publications. Another strength is the modified Mediterranean diet score specifically created for the MDCS based on the Med Diet Score used for the PREDIMED study, which has been validated as an accurate measurement of adherence to Mediterranean Diet.

Previous studies on diet quality and incidence of dementia disorders have shown varying results. In a large prospective cohort study (n=10,308), with a median follow-up time of 24.8 years, neither the quality of mid-life diet nor the Mediterranean diet were associated to incident all-cause dementia, which was confirmed by another prospective and longitudinal study with 20 years of follow-up including 13,588 participants showing no association of diet quality and further development of dementia or cognitive decline. Another study by Hosking et al. found no associations between the Mediterranean diet and cognitive decline or dementia, they could however show an association between MIND (Mediterranean-DASH Intervention for Neurological Delay) diet and cognitive decline as well as dementia, in 1220 participants over a 12-year period. A systematic review including 32 studies, concluded
that adherence to a Mediterranean diet may contribute to better cognitive performance and
decreased risk of developing dementia. This review reflects the current state of knowledge,
since the studies included are very heterogeneous in their designs. A majority of them used
retrospective food frequency questionnaires, which may be associated with misreporting by
the participants considering difficulties to remember historical details about food intake many
years or even decades back in time.\textsuperscript{30} In addition, a majority of the studies included in the
review are based on dietary habits in elderly populations (>65 years). Considering the
relatively high prevalence of prodromal dementias in such populations there is a risk of
reversed causality. Early cognitive decline with possible mood changes could also affect
dietary lifestyle habits.\textsuperscript{31} Hence, inclusion of an older population may bias the correlation
between diet quality and cognitive decline. Additionally, the varying follow-up time between
studies might be one reason of the heterogeneous study results regarding dietary habits and
incidence of dementia disorders. However, the authors of the systematic review concluded
and emphasized the importance of confirmation based on large longitudinal epidemiological
studies with prospective registration of dietary habits, thus highlighting the value of the
present study. As expected, known cardiovascular risk factors such as coronary event or
stroke, diabetes and arterial hypertension were all more common at baseline in the group with
incident dementia (Table 1).

The current study does not exclude a possible association between diet quality
and subsequent development of dementia. However, the present Swedish dietary
recommendations, which are in line with those in the UK and US, or according to the
Mediterranean dietary pattern, could not be confirmed to be associated with prevention of
dementia. There is however a risk of self-reported dietary and lifestyle habits being
misreported to some extent. There is also a possible risk of alteration in dietary habits, even
though dietary habits remain relatively stable during life. Previous studies on diet and CSF Aβ
measures are either cross-sectional or have short follow-up time (4 weeks-1.2 years). This further highlights the importance of this study examining the association between dietary habits and later CSF Aβ-pathology, with 13 years of follow-up. However, one review, including 7 RCTs, 7 cross-sectional studies and one longitudinal study on diet and biomarkers of AD, concludes that adherence to Mediterranean diet and reduction of AD biomarkers, as well as high-glycaemic and high saturated fat diet, were all associated with an increase in biomarker levels of AD. A study by McEvoy et al. showed that adherence to the Mediterranean diet was associated with better cognitive performance in midlife. However, we enhance using dementia diagnoses as outcome is the most clinically relevant.

Considering that no systematic cognitive testing was available during follow-up (only available in medical records for those undergoing dementia work-ups according to routine clinical practice), and that the reviewed dementia diagnoses were retrieved from the National Patient Register, there could be an underestimation of the number of dementia cases. The advantage, however, is that all surviving participants were under risk for dementia during the study period and only those completing follow-up visits. Note also that to improve the quality of the dementia diagnoses, fulfilment of diagnostic criteria was validated retrospectively by trained physicians at the memory clinic. Dietary data was only collected at baseline, and there is a risk of alterations in dietary habits during follow-up. This was however somewhat accounted for by excluding participants who reported a substantial alteration in dietary habits at any time before baseline in sensitivity analysis, with the same results as in the main analyses. Although participants were followed for a median period of 19.8 years, we cannot rule out that even longer follow-up might have resulted in a slightly different result. Using vegetable oils instead of olive oil could be a limitation of the mMDS, however the vegetable oils in the mMDS are all of vegetable origin, with a high proportion of mono- and polyunsaturated fatty acids. Further, participants with CSF samples were not
randomized, but recruited based on clinical indications, which is a limitation of the study. Although multiple baseline characteristics were adjusted for, additional possible confounding factors cannot be ruled out, such as health selection bias. Randomized controlled trials are needed to provide additional evidence regarding the potential role of diet in relation to AD-pathology. However, it is probably not feasible to design a 20-year randomized controlled trial with strict dietary habits to adhere to.

**Conclusion**

Adherence to conventional dietary recommendations or to a modified Mediterranean diet during midlife, were not associated with a lower incidence in all-cause dementia over a 20-year period, nor was the diet associated with AD dementia, accumulation of Aβ pathology or to Vascular dementia. Large intervention studies are needed to clearly understand if diet quality can affect incidence of dementia disorders, even if the results from this study together with other large prospective longitudinal studies\textsuperscript{27,28} implicate this will not be the case.

**REFERENCES**


Figure 1. Flow chart describing the MDCS population at baseline and follow-up.

Table 1. Baseline Characteristics of the Study population in 1991-1996

<table>
<thead>
<tr>
<th></th>
<th>No incident dementia(^a) (N=26,082)</th>
<th>Incident all-cause dementia(^a) (N=1,943)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, (SD), y</td>
<td>57.6 (7.5)</td>
<td>64.3 (5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, women</td>
<td>15,806 (61%)</td>
<td>1186 (61%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Education level, (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school ((&lt;8) years)</td>
<td>10,739 (41.2%)</td>
<td>1,037 (53.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9-12 years</td>
<td>9,185 (35.2%)</td>
<td>638 (32.8%)</td>
<td>0.034</td>
</tr>
<tr>
<td>(\geq) 13 years</td>
<td>6,158 (23.6%)</td>
<td>268 (13.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total energy intake, mean (SD), (kJ/day)</td>
<td>9,540 (2730)</td>
<td>9,380 (2760)</td>
<td>0.005</td>
</tr>
<tr>
<td>Swedish Dietary Guidelines Score 0-5, mean (SD)</td>
<td>1.94 (1.29)</td>
<td>1.98 (1.26)</td>
<td>0.08</td>
</tr>
<tr>
<td>Swedish Dietary Guidelines Score Groups, (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 points</td>
<td>10,647 (40.8%)</td>
<td>745 (38.3%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2-3 points</td>
<td>12,006 (46.0%)</td>
<td>941 (48.4%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4-5 points</td>
<td>3,429 (13.1%)</td>
<td>257 (13.2%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Modified Mediterranean Score 0-10, mean (SD)</td>
<td>2.65 (1.25)</td>
<td>2.65 (1.20)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
<table>
<thead>
<tr>
<th>Study Measurements</th>
<th>n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Mediterranean Score Groups, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 points</td>
<td>4,514 (17.3%)</td>
<td>319 (16.4%)</td>
</tr>
<tr>
<td>2-4 points</td>
<td>19,560 (75.1%)</td>
<td>1,501 (77.3%)</td>
</tr>
<tr>
<td>5-10 points</td>
<td>2,008 (7.7%)</td>
<td>123 (6.3%)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>7,509 (28.8%)</td>
<td>413 (21.3%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>8,812 (33.8%)</td>
<td>671 (34.5%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>9,750 (37.4%)</td>
<td>859 (44.2%)</td>
</tr>
<tr>
<td>Physical activity (METH/week)^b, mean (SD)</td>
<td>3.34 (1.20)</td>
<td>3.38 (1.20)</td>
</tr>
<tr>
<td>Alcohol consumption, g/day, mean (SD)</td>
<td>10.90 (12.80)</td>
<td>8.86 (10.90)</td>
</tr>
<tr>
<td>Body Mass Index^c, mean (SD)</td>
<td>25.72 (3.97)</td>
<td>26.08 (3.96)</td>
</tr>
<tr>
<td>History of coronary event or stroke, n (%)</td>
<td>739 (2.8%)</td>
<td>80 (4.1%)</td>
</tr>
<tr>
<td>Diabetes at baseline, n (%)</td>
<td>4,816 (18.5%)</td>
<td>405 (20.8%)</td>
</tr>
<tr>
<td>Hypertension at baseline, n (%)</td>
<td>4,387 (16.8%)</td>
<td>452 (23.3%)</td>
</tr>
<tr>
<td>Time of follow-up, mean (SD), y</td>
<td>18.5 (4.88)</td>
<td>NA</td>
</tr>
<tr>
<td>Time from baseline to event, mean (SD), y</td>
<td>NA</td>
<td>14.6 (4.72)</td>
</tr>
<tr>
<td>Incident coronary event or stroke^d, n (%)</td>
<td>4,879 (18.7%)</td>
<td>571 (29.4%)</td>
</tr>
<tr>
<td>Incident diabetes at re-examination^e, n (%)</td>
<td>711 (2.7%)</td>
<td>43 (2.2%)</td>
</tr>
</tbody>
</table>
a End of follow-up on December 31, 2014 or death.

b Physical activity as metabolic equivalent hours/week (METh/week). One METh is defined as the metabolic intensity when a person is at rest. METh/week was computed by multiplying time (hours) spent on each activity by the respective metabolic equivalent task (intensity) factor (MET).

c Calculated as weight in kilograms divided by height in meters squared.

d Until end of follow-up December 31, 2014.

e Re-examination 2007-2012
<table>
<thead>
<tr>
<th></th>
<th>All-Cause Dementia</th>
<th>Alzheimer’s Disease Dementia</th>
<th>Vascular Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>64.3 (5.9)</td>
<td>64.4 (5.8)</td>
<td>65.0 (5.7)</td>
</tr>
<tr>
<td><strong>No. of cases/Total No.</strong></td>
<td>1,943/28,025</td>
<td>1,137/28,025</td>
<td>461/28,025</td>
</tr>
<tr>
<td><strong>Adjusted Hazard Ratio (95% CI)</strong></td>
<td>Model 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Model 1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Swedish Dietary Guidelines Score 0-5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.98 (0.95-1.02)</td>
<td>0.99 (0.95-1.03)</td>
<td>0.99 (0.95-1.04)</td>
</tr>
<tr>
<td>Swedish Dietary Guidelines Score 0-1 (worst)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>[Reference]</td>
<td>[Reference]</td>
<td>[Reference]</td>
</tr>
<tr>
<td>Swedish Dietary Guidelines Score 2-3 (intermediate)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.00 (0.90-1.10)</td>
<td>1.02 (0.92-1.12)</td>
<td>1.07 (0.94-1.21)</td>
</tr>
<tr>
<td>Swedish Dietary Guidelines Score 4-5 (best)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.93 (0.81-1.08)</td>
<td>0.95 (0.82-1.10)</td>
<td>1.03 (0.85-1.23)</td>
</tr>
</tbody>
</table>
a Estimated using Cox Proportional Hazard models. Participants were followed from baseline (1991-1996) until December 31, 2014, or date of death.

b Model 1 adjusted for sex, age, education, dietary assessment method, season and total calory intake.

c Model 2 adjusted for model 1 and additionally adjusted for smoking, physical activity, alcohol consumption and body mass index.

d Swedish Dietary Guidelines score examined as continuous measure, 0-5 points, (poor to good adherence to dietary recommendations).

e Swedish Dietary Guidelines score examined as three different groups, poor to good adherence to dietary recommendations (0-1 (reference), 2-3 and 4-5 points).
Table 3. Association between modified Mediterranean Diet Score and incident All-Cause Dementia, Alzheimer’s Disease Dementia and Vascular Dementia

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Dementia</th>
<th>Alzheimer’s Disease Dementia</th>
<th>Vascular Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>64.3 (5.9)</td>
<td>64.4 (5.8)</td>
<td>65.0 (5.7)</td>
</tr>
<tr>
<td>No. of cases/Total No.</td>
<td>1,943/28,025</td>
<td>1,137/28,025</td>
<td>461/28,025</td>
</tr>
<tr>
<td>Adjusted Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.99 (0.96-1.03)</td>
<td>0.99 (0.94-1.05)</td>
<td>0.99 (0.94-1.05)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00 (0.96-1.04)</td>
<td>1.00 (0.94-1.04)</td>
<td>1.04 (0.96-1.12)</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.92 (0.81-1.04)</td>
<td>0.94 (0.83-1.06)</td>
<td>0.91 (0.77-1.07)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.91 (0.77-1.07)</td>
<td>0.95 (0.83-1.06)</td>
<td>0.91 (0.71-1.16)</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.93 (0.75-1.15)</td>
<td>0.95 (0.76-1.18)</td>
<td>0.90 (0.68-1.19)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.90 (0.68-1.19)</td>
<td>0.95 (0.76-1.18)</td>
<td>0.87 (0.66-1.16)</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.93 (0.75-1.15)</td>
<td>0.95 (0.76-1.18)</td>
<td>1.00 (0.65-1.55)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.90 (0.68-1.19)</td>
<td>0.95 (0.76-1.18)</td>
<td>1.09 (0.70-1.70)</td>
</tr>
</tbody>
</table>

*Estimated using Cox Proportional Hazard models. Participants were followed from baseline (1991-1996) until December 31, 2014, or date of death.

*Model 1 adjusted for sex, age, education, dietary assessment method, season and total calory intake.


\[ \text{Model 2 adjusted for Model 1 and additionally adjusted for smoking, physical activity, alcohol consumption and body mass index.} \]

\[ \text{Modified Mediterranean Diet Score examined as continuous measure 0-10 points, (poor to good adherence to modified Mediterranean dietary recommendations).} \]

\[ \text{Modified Mediterranean Diet Score examined as three different groups: Modified Mediterranean Diet Score 0-1 points reflect poor adherence, (reference), 2-4 points (intermediate adherence) and 5-10 points (best adherence).} \]
Association Between Dietary Habits in Midlife With Dementia Incidence Over a 20-Year Period
Isabelle Glans, Emily Sonestedt, Katarina Nägga, et al.
Neurology published online October 12, 2022
DOI 10.1212/WNL.0000000000201336

This information is current as of October 12, 2022

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://n.neurology.org/content/early/2022/10/12/WNL.0000000000201336.full">http://n.neurology.org/content/early/2022/10/12/WNL.0000000000201336.full</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td></td>
<td>All Cognitive Disorders/Dementia <a href="http://n.neurology.org/cgi/collection/all_cognitive_disorders_dementia">http://n.neurology.org/cgi/collection/all_cognitive_disorders_dementia</a></td>
</tr>
<tr>
<td></td>
<td>Alzheimer’s disease <a href="http://n.neurology.org/cgi/collection/alzheimers_disease">http://n.neurology.org/cgi/collection/alzheimers_disease</a></td>
</tr>
<tr>
<td></td>
<td>Vascular dementia <a href="http://n.neurology.org/cgi/collection/vascular_dementia">http://n.neurology.org/cgi/collection/vascular_dementia</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a></td>
</tr>
</tbody>
</table>