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# Dietary Patterns in Relation to Healthy Aging.

## The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

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# Dietary Patterns in Relation to Healthy Aging.

## The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

Introduction: Population aging is accelerating rapidly in Israel as well as worldwide necessitating adaptation of the health care system and consideration of new approaches that serve the specific needs of the elderly. In addition to cognitive decline, frailty is one of the most challenging expressions of physical and mental aging, a multidimensional syndrome of increased vulnerability. Several studies have shown that low intake of certain micronutrients and protein is associated with higher risk of frailty and cognitive impairment. However, whether global dietary patterns are involved in the etiology of the latter outcomes is unclear.

Methods and analysis: We are conducting, among elderly subjects who took part in "MABAT ZAHAV" (Israeli National Health and Nutrition Survey of the Elderly) in 2005-2006 (T1, N=1,852) an extensive follow-up interview (T2) that includes comprehensive geriatric assessment and evaluation of general health and quality of life. Diet quality is evaluated using the Healthy Eating Index (HEI) 2010, based on 24-hour diet recall measured at T1 and T2. Frailty is assessed using two different approaches: the phenotype framework and the accumulation of deficits model. Cognitive function is assessed by Mini Mental State Examination (MMSE) and cognitive decline by the difference between repeated measurements of MMSE. Multiple logistic regression models will be constructed to evaluate the role of dietary patterns in development of frailty and cognitive decline with inverse probability weighting used to minimize attrition bias. About 600 subjects are expected to be interviewed by the end of 2019.

Ethics and dissemination: Ethical approval was obtained from the Helsinki Committee of Sheba Medical Center, Tel Hashomer, Israel and the Ethical Committee of Tel-Aviv University. All participants will sign an informed consent form. The findings of the study will be published in peer-reviewed journals.

Keywords: dietary patterns; epidemiology; elderly; frailty; longitudinal studies

## Strengths and limitations of this study

- A cohort study design with broad-spectrum data and more than a decade long follow-up will allow us to evaluate trajectories of various functioning, cognitive, behavioral and social health outcomes, and assess their determinants in the elderly population of Israel.
- Only few studies have explicitly examined the concept of robust aging among the oldest-old, the most rapidly expanding segment of the population, and investigated its heterogeneity.
- Selection bias due to death, loss to follow-up and non-response.
- Nutritional assessment is based on a single 24-hour dietary recall.
- Self-reported data leading to misclassification bias.

## Background

### Healthy aging

Population aging is accelerating rapidly in Israel as well as worldwide necessitating adaptation of the health care system and consideration of new approaches that serve the specific needs of the elderly [1]. According to current forecasts the percentage of persons 65 years and older will increase from 8.5% at 2015 to 19% by 2030 [2]. The concept of healthy aging is generally described as optimizing opportunities for improving and preserving health and physical, social, and mental wellness; independence; quality of life; and enhancing successful life-course transitions [3]. While this definition depicts healthy aging or successful aging as a complex process of adaptation to changes across the lifespan, the concept needs to be looked at in terms of a measurable outcome that can be empirically validated [4]. Despite the differences in healthy aging definitions, there is some consensus in the studies that 'successful ager' outcome should measure the capacity to function well in domains of cognitive, physical and mental well-being [4].

### Frailty

Frailty is internationally recognized as an important medical syndrome that describes the heterogeneity of vulnerability in older people [5]. Frail older persons are at high risk of accelerated physical and cognitive functional decline, disability, and death [6]. The concept of frailty adopts an integrative approach which represents general properties of aging and health rather than particular functional deficiency or decline [7]. Assessment of frailty has implications both for the individual and on society at large, forecasting healthcare use [8 9] and providing opportunities for preventive intervention [10 11], thus making it a key issue in chronic disease management and healthy aging [12 13].

Studies show that an assessment of frailty can delay the development of disability and reduce the need for nursing among elderly people living at home [7]. Based on 21 cohorts involving 61,500 participants, on average, 11% of community-dwelling subjects aged 65 and older are defined frail and another 42% prefrail [14]. Nevertheless, the reported prevalence differed substantially, ranging from 4% to 59% due to different definitions and measurements of frailty status. Methods to measure frailty vary widely throughout the literature [5 15-19], with two principal models of frailty emerging: **(1)** The Fried and colleagues' *Biological Phenotype* framework [15], which conceptualizes frailty as a biologic syndrome characterized by a decline in overall function and loss of resistance to stressors. This model is comprised of five physical indicators including low physical activity, weak grip strength, slow walking speed, exhaustion, and unintentional weight loss.
**(2)** The Rockwood and colleagues' *Accumulation of Deficits* Index [20], which defines frailty as the cumulative effect of individual deficits. Under this model, frailty is measured by ~40 parameters of symptoms, signs, disease states and disabilities, collectively referred to as deficits. The index is a calculation of the presence or absence of each deficit as a proportion of total [8].

**Cognitive decline**

The field of aging and dementia is focusing on the characterization of the earliest stages of cognitive impairment. Mild cognitive impairment (MCI) is a recently described syndrome that is currently thought of as a transition phase between healthy cognitive aging and dementia [21]. Prevalence rates for age-associated memory impairment in population-based studies range from 17% to 34%, mostly vary as a result of different diagnostic criteria as well as different sampling and assessment procedures [22]. Clinical study results indicate that elderly individuals with MCI will progress to Alzheimer's Disease (AD) at a rate of 10% to 15% per year, compared with healthy control subjects who convert at a rate of 1% to 2% per year [23], making it an area of intense interest for theoretical and practical reasons. A widely recognized instrument for detection of cognitive impairment is the Mini Mental State Examination (MMSE) [24 25]. The MMSE consists of thirty questions and has a maximum score of 30 points. Cognitive decline definition among prospective studies varies [26] with a more commonly used method which define cognitive decline as the 10% of the sample who declined the most (i.e. the 90$^{th}$ percentile of decline). Such a population-based cutoff point has been shown to be sensitive and specific indicator of cognitive decline [27] and has been used in different studies [28-31].

**Nutrition**

Nutrition is an important element of health in the older population that affects and is affected by the aging process [32 33]. Malnutrition is highly prevalent among the elderly and associated with a general

decline in physical and mental functioning, higher hospitalization rate and increased mortality [32]. Eating patterns of various cultures around the world have been associated with risk for chronic diseases [34]. Accordingly, several countries have issued dietary recommendations aimed at chronic disease prevention [35]. However, little is known about the interactive effects of dietary behavior and diet quality on overall risk, as food and nutrients are not eaten in isolation. Consequently, indices of dietary quality, patterns, and variety are increasingly used by nutritional epidemiologists [36]. The Healthy Eating Index-2010 (HEI-2010) [37] is such an index, originally released in 1995 and then updated in 2010 by the US Department of Agriculture (USDA) as a measure of diet quality. The concept of nutritional deficiency as a determinant of frailty development is not new but whether it is a predictor or consequence of frailty has not been investigated adequately [38]. Several studies have shown that low intake of certain micronutrients and protein is associated with higher risk of developing frailty. However, very few studies have assessed the effect of overall dietary patterns on frailty [39]. Two studies have suggested that increasing adherence to Mediterranean diet (MD, a diet characterized by high intake of fish, vegetables, legumes, fruits, cereals, and unsaturated fatty acids [40]) is associated with decreasing risk of frailty among community-dwelling older adults in Spain and Italy [41 42]. In both studies, however, the MD was defined from sample-specific scores; thus, only the relative but not the absolute effect of MD was assessed, and the results of these studies are difficult to compare across populations. In addition, it was recently demonstrated that higher adherence to MD is associated with lower AD risk [43 44].

## Research Objective

### General objective

Investigate the relation between dietary patterns and healthy aging.

### Specific aims

**A.** Develop a frailty index based on "Mabat Zahav" data (T1) and evaluate its association with cause-specific mortality categories.

**B.** Investigate long-term trajectory of dietary patterns and nutritional status among study participants and examine its determinants.

**C**. Assess development of frailty among current study participants and examine its determinants, particularly dietary patterns.

**D**. Assess development of cognitive decline among current study participants and examine its determinants, particularly dietary patterns.

## Methods/Design

### Research design

The study employs a cohort study design. It constitutes the second interview (T2) of Mabat Zahav study- briefly described in the following section [45]. The study questionnaire duplicates most parts of the original (T1) interview (Fig. 1). In addition, measurements pertaining to frailty status are performed, as well as multidimensional scale of perceived social support (MSPSS) [46], geriatric depression scale (GDS) [47] and the short form of health-related-quality of life (SF-12) [48]. The HEI-2010, a measure of diet quality, is retrospectively assessed at T1 and, prospectively, at T2 in order to assess changes in diet quality and composition. Frailty at T1 is retrospectively assessed through the Rockwood and colleagues' Deficit Index [20 49] and prospectively at T2 by both the Deficit Index and the Fried and colleagues' Biological Phenotype framework [15]. The former will be developed according to published criteria [50]. Follow-up of cancer and mortality incidence, overall and across specific categories, will be conducted among T1 participants through linkage to the Israeli National Cancer Registry (INCR) and the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers.

**"Mabat Zahav" survey – study population**

The First National Health and Nutrition Survey of the elderly aged 65 and over in Israel ("Mabat Zahav") was carried out in 2005-2006 by the Israel Center for Disease Control (ICDC) and the Nutrition Department of the Israel Ministry of Health. The survey population was a random sample of Israeli citizens age ≥ 65 years old. The sampling framework was provided by the two major health funds, Clalit Health Services and Maccabi Health Services, which represent 86.3% of all the elderly citizens in Israel. Oversampling was carried out in the Arab population to ensure a sample large enough to carry out statistical analyses and comparisons with the Jewish sector. The survey included 1,852 participants (1,536 Jews and 316 Arabs) residing in Israel, in the community who had lived in the country for at least one year in urban and rural settlements with more than 20,000 residents. Exclusion criteria included: significant cognitive reduction-MMSE<17, current hospitalization for more than 6 months, hospitalization in a psychiatric institution, and hospitalization in a long-term-care institution. Survey methods included a personal interview in the interviewees' homes or sheltered accommodation using a structured questionnaire. The interviews were held in multiple languages and the questionnaires were translated accordingly: 1277 (69%) interviews took place in Hebrew, 316 (17%) in Arabic, 257 (14%) in Russian and 2 (0.1%) in English. The data collected on the survey included information regarding health and nutrition status, health behaviors (physical activity, alcohol consumption, medication use, use of nutrition supplements), knowledge and attitudes regarding nutrition, and utilization of health services among this population [45]. All data collected from 1,799 subjects are available on-line at the ministry of health government web site [51].

**Exclusion criterion in current research stage:**

Significant cognitive reduction as measured by MMSE score of less than 17 or inability to communicate.

**Sample size**

Among T1 initial participants (1,852), 1,799 (1,499 Jews and 300 Arabs) questionnaires were included in the survey final analysis. Forty-six participants (29 Jews and 17 Arabs) had a MMSE score of less than 17 (after adjustment for age and education) and seven questionnaires were only partially completed and therefore excluded from the statistical analysis. According to the mortality registry of the Ministry of Health, 1,115 participants were alive in February 2017. We assume that 25% of candidates will be unable to participate due to either exclusion criteria or severe medical condition and another 20% could not be contacted due to address or telephone number changes. We expect a response rate of 55%-60% among the remaining candidates for the T2 interview, and so about 600 subjects are expected to be re-interviewed (Fig.2). Our efforts to maximise recruitment include the following steps:

Disconnected phone numbers and no response: **a.** Locating adress changes via the Ministry of Interior database. **b.** Conducting search by the Israeli non-commercial telephone directory according to city of residence and family name only (in case of incorrect street name). **c.** Conducting 10 attemaps to contact each non-response on different days and hours.

Refusal: We are trying to encourge cooperation by: **a.** Offering to conduct interviews 7 days a week, morning times and afternoons. **b.** Offering to divide the interview to two separate times, in case the length of the interview is a concern for the participant. **c.** Request to try re-appeal in a few weeks or month.

**Data collection**

A personal interview is conducted in the interviewees' homes by trained interviewers using a structured questionnaire. Anthropometric measurements are performed using standardized protocols. Interviews are conducted in Hebrew, Arabic or Russian. Estimated time of an interview is an hour and a half. In case the participant is unable to complete the questionnaire by himself/herself, but still meets inclusion criteria, information from a proxy is obtained regarding dietary intake, chronic diseases and co-morbidities, activities of daily living (ADL), sociodemographic status and medication use. The proxy interview does not include the following assessments: GDS, SF-12, MSPSS and self-rated health. All data (except the 24-hours dietary recall) are collected using KoBotoolbox [52] software which is a freely available application to design surveys for data collection through smart devices and run on android based platforms. The data are exported into password protected Excel file on a daily basis. All responses are typed directly during the interview through Lenovo TAB2 A10-30 tablet. The 24-hours dietary recall is hand written and typed later to

"Tzamert" program [53], an Israeli nutrient data program, which enables recording of food intake and calculation of nutrient intake. In case of any technical difficulties the questionnaire is completed manually by the interviewer. A pilot study (n=30) was conducted, after which questionnaires, research tools and protocol were finalized.

Exposure variable: The HEI-2010 score at baseline (T1): Dietary data from the 24-hour dietary recall questionnaire was entered into the "Tzamert" program. The program uses the nutrient data in the BINAT program- the Israeli nutrient database which is maintained and updated by the Nutrition Department of the Ministry of Health. A HEI-2010 score [36 54] will be calculated for T1 and T2 interviews separately. The HEI-2010 has twelve components, nine of which assess adequacy of the diet, including 1) total fruit; 2) whole fruit; 3) total vegetables; 4) greens and beans; 5) whole grains; 6) dairy; 7) total protein foods; 8) seafood and plant proteins; and 9) fatty acids. The remaining three: refined grains, sodium, and empty calories, assess dietary components that should be consumed in moderation. For each component, the respondents receive a minimum score of 0 and a maximum score of 5 or 10 (for perfect adherence to recommendations); intermediate degrees of adherence are calculated proportionately. Thus, the overall index has a range from 0 (worst) to 100 [36 54].

Nutritional status assessments:

(1) Dietary recall: The multiple-pass 24-hour dietary recall questionnaire is administrated**.** The method was originally developed by the USDA in order to limit the extent of underreporting that occurs with self-reported food intake [55]. The interviewer uses three distinct passes to gather information about a subject's food intake during the preceding 24 hours. The first pass is termed the *quick list*, here the interviewees are asked to recall all they had eaten and drunk in the 24-hour period that preceded the interview. The second pass is termed the *detailed description*. In this pass the interviewees are asked to clarify any foods mentioned in the quick list. The third pass is termed the *review*. The interviewer reviews the list of foods mentioned and probes for additional eating occasions and clarifies food portion sizes [55]. In order to assist the interviewees in identifying food types and quantities during the interview, the interviewers use the "Food and Food Quantities Guide" which is partially based on the Food Guide of the USDA. The guide includes detailed questions on foods, as well as many photographs of Israeli foods. In order to facilitate quantification of amounts consumed, the interviewers use, in addition to the guide, identification aids such as a measuring cup, tablespoon and teaspoon.

(2) Food security: Household food security is defined as a situation whereby all household members have access at all times to a food supply which is adequate for a healthy active life. Food security is assessed using the short 6-item food security USDA questionnaire [56].

(3) Malnutrition risk: Modified Mini Nutritional Assessment– Short Form (MNA-SF) [57]. The 6-item questionnaire is a nutritional screening tool that assess malnutrition risk.

Outcome variables:

Frailty assessment: Frailty at T1 and T2 is assessed by the *Deficit Index* model [20 49]. Under this model, frailty is measured by ~40 parameters of symptoms, signs, disease states and disabilities, collectively referred to as deficits. Adapting the Rockwood index of accumulation of deficits method [7] with T1 data, a Frailty Index (FI) was developed comprising 33 variables. The FI at T2 will comprise the same variables and will serve as outcome measure. The FI is a calculation of the presence or absence of each deficit as a proportion of the total. Dichotomous items are coded as 0 if the deficit is absent and as 1 if it is present, while ordinal variables are graded into a score between 0 and 1 (0 representing no impairment, 0.5 for minor impairment, and 1 for major impairment). Scores are then summed up and divided by the total number of variables, yielding a frailty index between 0 and 1, with 1 representing the greatest frailty (a threshold of ≥0.25 is typically used to define frailty) [58]. Frailty at T2 is additionally assessed by the *Biological Phenotype* model [15]. Frailty using this instrument is identified by the presence of three or more of the following components: 1. Shrinking: weight loss, unintentional, of more than 4.5 Kg, or more than 5% of body weight, in previous year; 2. Weakness: grip strength in the lowest 20% (adjusted for sex and body mass index); 3. Poor endurance and energy: as indicated by self-report of exhaustion; 4. Slowness: the slowest 20% of the participants in the sample, based on time of a 5-meter walk (adjusted for sex and standing height); 5. Low physical activity level: a weighted score of kilocalories expended per week will be calculated based on a Physical Activity Scale for the Elderly (PASE) questionnaire [59]. The lowest quintile of physical activity will be identified for each gender.

Cognitive assessment**:** Cognitive status is evaluated using the MMSE [24], which can be administered in 5-10 minutes. The maximum score is 30. The questions typically have been grouped into seven categories, each representing a different cognitive domain or function: orientation to time (5 points); orientation to place (5 points); registration of three words (3 points); attention and calculation (5 points); recall of three words (3 points); language (8 points) and visual construction (1 point) [60]. The MMSE scores will be education- and age-standardized [61]. Some participants cannot complete test items due to physical disability. Items that the participant cannot complete will not be included in the

total score. The MMSE will be scored out of the items that can be tested [62]. Cognitive impairment will be defined as a score < 24 [63]. Cognitive decline will provide the outcome variable and will be calculated as the MMSE score difference between 2005 and 2017.

Other covariates:

Health status evaluation: The questionnaire includes data on self-rated health (current status and recent trajectories), chronic diseases and co-morbidities (e.g. cardiovascular diseases, Parkinson's disease, respiratory diseases, renal disease, cancer, glaucoma and cataract, diabetes mellitus, osteoporosis, hypertension). In addition, the questionnaire includes demographic details, alcohol consumption and smoking habits information.

Assessment of disabilities: Function is assessed by the Katz scale of Activities of Daily Living [64] based on ability to dress, shower/bathe, sit down and rise from a chair, eat and go to the bathroom. The maximum score is 15, with a score of 5 indicating "no functional limitations", a score of 6-10 indicating some functional limitations, and a score of 11 or more indicating several functional limitations.

Psychosocial assessments: Assessments include depression, perceived social support and health-related quality of life (SF-12). Depression is evaluated via a 5-item short form of the Yesavage geriatric depression scale (GDS) [47]. A score of 2 or higher indicates possible depression. Social support is assessed through the Multidimensional Scale of Perceived Social Support (MSPSS) [65], a 12-item questionnaire designed to measure perceptions of support from three sources: family, friends and a significant other (4 items for each source). Answers are given on a 1-7 scale. Weighted scores are calculated by averaging the specific items, each scale (source) individually and the entire questionnaire. A high score represents a high level of perceived social support. Health-related quality of life is evaluated via a short form of a multidimensional measure of health-related quality of life SF-12 [48], physical (PCS) and mental (MCS) component scores will be constructed from SF-12, using standard (U.S.) and country-specific scoring algorithms.

Drugs: The participants are asked about any medication use on a regular basis (prescription as well as over-the-counter drugs). In the preliminary letter, the participants are asked to prepare their regular medication list. Medications are coded using the ATC (Anatomical Therapeutical and Chemical) system, developed by the World Health Organization (WHO) [45].

Anthropometric measurements: Include standing height and weight, ulna length (to calculate height, using recognized formulae), waist and mid upper arm circumference. Weight measurements are carried out using an analog scale suitable for weighing up to 130 kg, with accuracy to 0.5 kg. The scales are placed on an uncarpeted floor and calibrated before weighing. Height is measured using a spring coil measuring tape. Waist circumference is measured using a flexible tape, with ability to measure up to 150 cm, at the narrowest part of the torso, where a "fold" is created when bending sideways [45]. Mid upper arm circumference is measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromion) using a flexible tape [66].

Blood pressure and pulse measurements: The interviewers are conducting blood pressure and pulse measurements using an electronic monitor. The measurements are carried out according to a protocol based on recommendations of the American Heart Association [67]. Sitting blood pressure and pulse are measured in the right arm and is carried out twice, with a minute rest in-between. In case of a difference of 10% or more between measurements of either systolic or diastolic pressure, a third measurement is carried out. The final value will be the mean of measurements.

Cancer incidence and cause of death: Original participants were linked to the INCR and the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers. Data supplied by the INCR include diagnosis code and date of diagnosis. Mortality information is managed by the Ministry of Health. Since 1999, deaths are coded according to the International Classification of Diseases, Tenth Edition (ICD-10). Cause-specific mortality categories were divided to cardiovascular disease (CVD) deaths and non-CVD deaths. According to classification used by the American Heart Association [68], CVD death are divided into 3 categories: coronary heart disease (CHD), diseases of the heart and diseases of the circulatory system (ICD-10: I00-I99).

**Quality assurance**

Quality assurance is carried out in various ways: (1) A pilot study (n=30) was conducted, after which questionnaires and research tools were finalized; (2) Interviewer training: A 2-day seminar were designed and included standard procedures of administrating research questionnaires, performing anthropometric measurements and handling data in general; (3) All interviews (under interviewee consent) are recorded; (4) The study coordinator randomly monitor 5-10% of all interviews; (5) Intermediate data analysis will include division per each interviewer in order to assess potential

differences; (6) Dietary data quality assurance includes: ***a.*** a food recall check: time sequence, completeness of information, matching of the items in the "Quick List" with those in the "Comprehensive List", and ***b***. following data entry into the Tzamert program, testing will be performed for outliers, inappropriate quantities, lack of correlation between meal times and types, and missing quantities and incorrect coding.

**Statistical analysis according to specific aims**

Analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC), IBM SPSS version 25 (SPSS, Chicago, IL) and R version 3.2.3 (R Development Core Team).

**A.** Frailty categories assessed at baseline (T1; frail vs. Robust) will serve as the exposure variable. Baseline characteristics across frailty index categories will be compared by chi-squared test for categorical variables and student-t test for continuous variables. Cox proportional hazards regression models [69] will be fitted to evaluate the hazard ratios for death and other time-to-event outcomes associated with baseline exposure groups. Several adjustment methods will be applied including traditional multivariable adjustment and propensity score adjustment [70]. The incremental discriminatory ability of frailty index over demographic and SES variables in predicting death during a 12-year follow up will be evaluated by the c-statistic. Assessing the c-statistic and its corresponding standard error from Cox proportional hazards models will be performed with a methods proposed by Harrell et al [71].

**B.** Descriptive statistics will include prevalence of malnutrition risk as assessed at T2. Current nutritional consumption (T2) will be compared with recommendations using student-t test for continuous variables [72]. Characteristics across nutritional consumption across HEI categories (e.g., tertiles) will be compared by chi-squared test for categorical variables and analysis of variance for continuous variables**.** In order to investigate different determinants of longitudinal changes in diet quality (as measured by the difference between two HEI scores), we will use generalized linear model [73] and multivariable logistic regression models, as appropriate. Of the 1,799 participants in the original survey, many are no longer able to participate in T2 interview (death, loss to follow-up, non-response). Because frailty status could not be assessed among the latter group, selection bias is introduced [74]. This bias will be addressed through an adaptation of a marginal structural model, applying inverse probability weights [74 75]. Accordingly, the probability of original participants to take part at the second interview will be estimated. Each observation will then be weighted by the reciprocal (i.e., the inverse) of the predicted probability of participating at T2.

**C.** Frailty among current study participants (T2) will be assessed by two methods and Weighted Kappa will be used to assess the agreement in the results of the two methods that measure frailty [76]. Baseline characteristics across HEI categories (lower vs. upper diet score tertiles) as measured at T1 will be compared by chi-squared test for categorical variables and analysis of variance for continuous variables. The predictive role of nutritional indices in long-term incidence of frailty will be assessed using multivariate logistic regressions models [77]. Frailty categories, assessed at follow-up (T2), will be treated as dichotomous outcome (frail vs. robust). We will exclude participants who were frail at baseline. Selection bias will be addressed through an adaptation of a marginal structural model, applying inverse probability weights [74 75] as described above. Adjustment will be made for sociodemographic, clinical, and psychosocial variables, via either multivariable adjustment or propensity score [78].

**D.** In order to investigate dietary patterns and their potential role in cognitive longitudinal changes we will consider several methods for defining cognitive decline as they vary considerably [26] and compare results using different definitions. We will exclude participants with cognitive impairment at baseline (MMSE score < 24). The predictive role of nutritional indices in cognitive changes will be assessed using generalized linear model [73] or multiple logistic regressions models [77] depending on cognitive decline definition method used. Several adjustment methods will be applied including multivariable adjustment or propensity score[78]. Selection bias will be addressed through an adaptation of a marginal structural model, applying inverse probability weights [74 75] as described above.

**Approach to missing data**

Missing values for the variables comprising the frailty index will be imputed using multiple imputation methodology [79]. The number of complete (imputed) datasets will be defined by the following formula: $(1+\lambda/m)^{-1}$= *efficiency*, where $\lambda$ is the fraction of missing information and *m* the number of datasets to impute. We will assume an efficiency of 0.975. Missing values will be replaced by imputed values based on models incorporating demographic, socioeconomic, psychosocial, and clinical variables. The results of these datasets will then be combined using Rubin's rules [79].

**Estimated statistical power**

Among 1,800 initial participants, some 1,115 survived so far. Assuming a response rate of 55% for the T2 interview, about 600 subjects are expected to be re-interviewed. Considering an estimated average age of 84 years in the T2 interview, with a reported frailty prevalence of over 35% at that

age [80], about 250 frail subjects can be expected. This sample size is sufficient for detecting an adjusted odds ratio for frailty of ≤ 0.60 between the upper vs. lower HEI score tertiles (significance level at 5% and power of 80%). A previous study showed after a 6-year follow-up, that higher adherence to MD diet was associated with lower odds of developing frailty [OR = 0.30 (95% CI: 0.14, 0.66)] [42].

**Patient and Public Involvement**

Patients and or public were not involved.

**Ethical aspect**

Ethical approval for the study was obtained from the Helsinki Committee of Chaim Sheba Medical Center at Tel Hashomer and the Ethical Committee of Tel-Aviv University (Appendix A). Potential participants receive a preliminary letter with a description of the study, a request to participate and an announcement that telephone contact would be made in the near future. In addition, the letter provides the telephone number of the research coordinator for further questions. After a minimum of two weeks, potential participants are contacted by telephone in order to set an interview appointment for those who agree to participate. The interview does not involve clinical procedures and no human biological specimens are collected. Therefore, participants' burden is minimal. Each interviewee is asked to sign an informed consent form.

**Dissemination**

The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

## Discussion

The ILSA sets out to transform a large national survey of the elderly with a broad-spectrum data into a cohort study with specific age-related questionnaire including comprehensive geriatric assessment, evaluation of general health and quality of life. Obtaining data at two points in time, more than a decade apart, allows us to evaluate long-term trajectories in elderly population and examine dietary trajectories in the context of healthy aging and adverse clinical outcomes. Participants' estimated current mean age of 84 years old, defined as the "oldest-old", have over past decades been the most rapidly expanding segment of the population in developed countries and also the most susceptible to disease and disability [81]. Only few studies have explicitly examined the concept of robust aging among the oldest-old and investigated its heterogeneity in functioning, cognitive abilities, diet

quality and nutritional status changes. Both frailty and cognitive decline are at the core definition of healthy aging and are highly prevalent in older people; still, as their status varies considerably among elderly people, important issues such as how they develop, are they preventable, and can they be detected reliably have yet to be defined. Examining the role of nutritional dietary pattern in the context of healthy aging and adverse clinical outcomes may help to broaden our knowledge regarding the elderly population, provide scientific basis on which policy makers can rely and pave the way for early therapeutic interventions.

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# Footnotes

## Authors' contributions

AG, study coordinator of the ILSA, drafted the manuscript, assisted in the conception of the study and led field activities and study monitoring; UG, co-investigator for the ILSA, conceived of the study concept and design and supervised the study; T Shohat, co-investigator of the ILSA and physician-in-charge of the study; LKB, principal investigator of MABAT ZAHAV survey; T Shimony, coordinator of MABAT ZAHAV survey; YG, principal investigator of the ILSA, conceived of the study concept and design and co-drafted the manuscript. All authors revised, reviewed and approved the final paper.

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## Competing interests

The authors declare that they have no competing interests.

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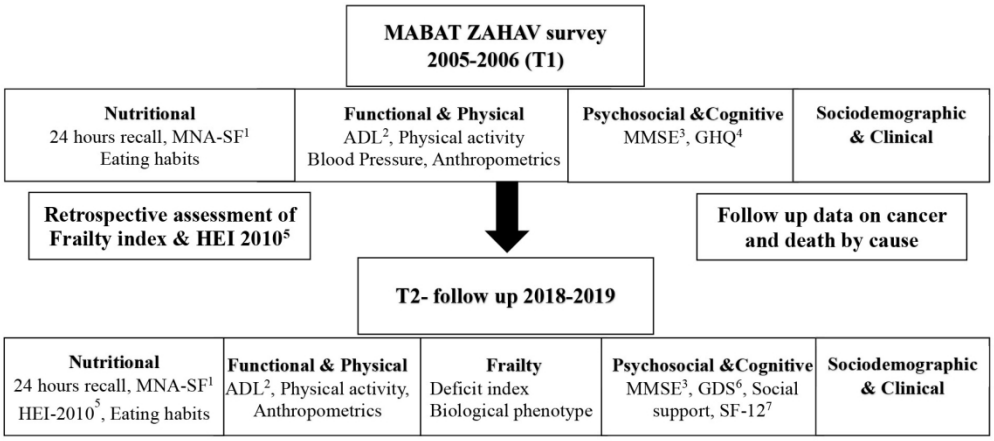


Figure 1. Research design sketch. [1]Mini Mental State Examination; [2]General Health Questionnaire; [3]Activities of Daily Living; [4]Mini Nutritional Assessment– Short Form;[5] Healthy Eating Index; [6]Geriatric Depression Scale; [7]Short Form of health-related-quality of life.

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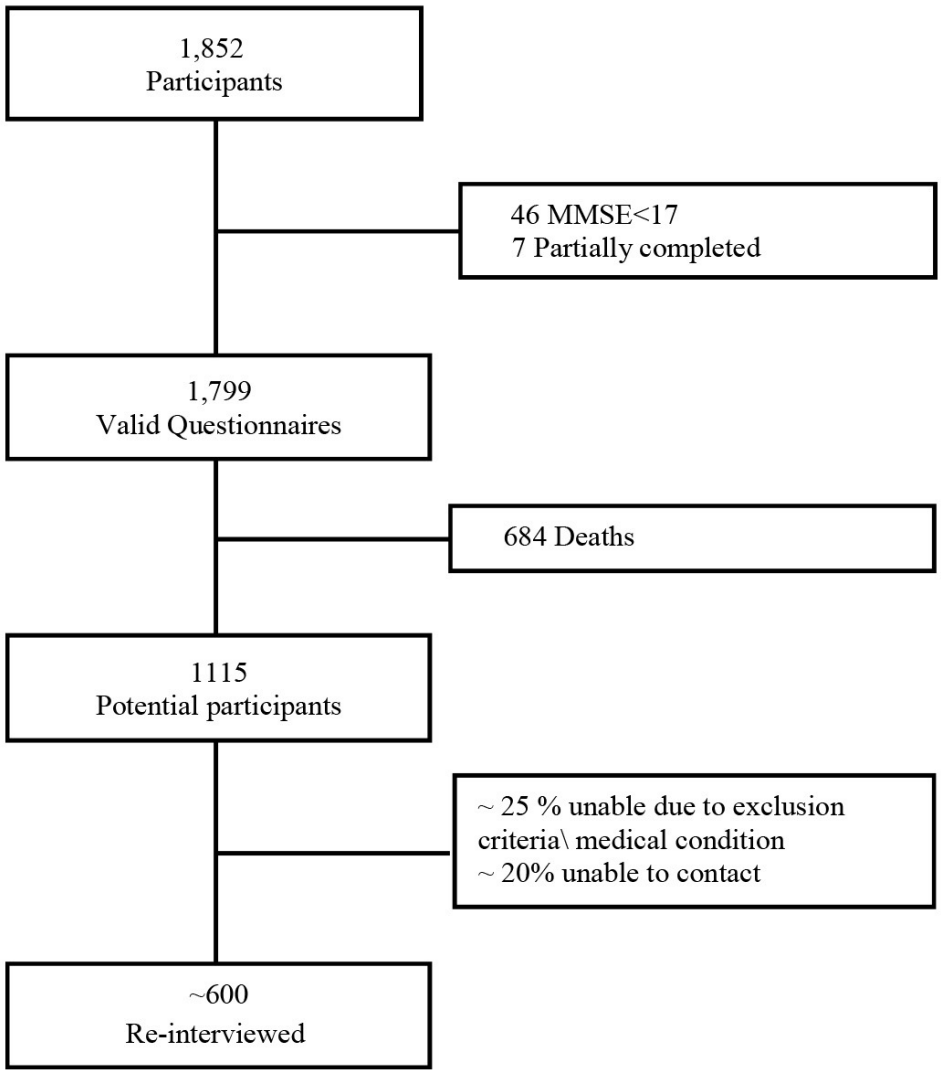


Figure 2. Sample size flow chart.

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# Dietary Patterns in Relation to Healthy Aging. The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.



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# Dietary Patterns in Relation to Healthy Aging.

## The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

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# Dietary Patterns in Relation to Healthy Aging.

## The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

Introduction: Population aging is accelerating rapidly in Israel as well as worldwide necessitating adaptation of the health care system and consideration of new approaches that serve the specific needs of older adults. In addition to cognitive function, frailty is one of the most challenging expressions of physical and mental aging, a multidimensional syndrome of increased vulnerability. Several studies have shown that low intake of certain micronutrients and protein is associated with higher risk of frailty and cognitive impairment. However, whether global dietary patterns are involved in the etiology of the latter outcomes is unclear.

Methods and analysis: We are conducting, among older adults subjects who took part in "MABAT ZAHAV" (Israeli National Health and Nutrition Survey of Older Adults) in 2005-2006 (T0, N=1,852) an extensive follow-up interview (T1) that includes comprehensive geriatric assessment and evaluation of general health and quality of life. Diet quality is evaluated using the Healthy Eating Index (HEI) 2010, based on 24-hour diet recall measured at T0 and T1. Frailty is assessed using two different approaches: the phenotype framework and the accumulation of deficits model. Cognitive function is assessed by Mini Mental State Examination (MMSE) and cognitive decline by the difference between repeated MMSE measurements. Different analytic methods will be applied to evaluate the role of dietary patterns in development of frailty and cognitive decline with inverse probability weighting used to minimize attrition bias. About 600 subjects are expected to be interviewed by the end of 2019.

Ethics and dissemination: Ethical approval was obtained from the Helsinki Committee of Sheba Medical Center, Tel Hashomer, Israel and the Ethical Committee of Tel-Aviv University. All participants will sign an informed consent form. The findings of the study will be published in peer-reviewed journals.

Keywords: dietary patterns; epidemiology; elderly; frailty; longitudinal studies

## Strengths and limitations of this study

- The study transforms a large national survey of older adults with a broad-spectrum data into a cohort study with a specific age-related questionnaire including comprehensive geriatric assessment.
- Obtaining data at two points in time, more than a decade apart, will allow us to evaluate long-term changes in older adults population and examine adverse clinical outcomes.
- Only few studies have explicitly examined the concept of robust aging among the oldest-old age group.
- Selection bias due to death, loss to follow-up and non-response.
- Misclassification bias due to self-report data and nutritional assessment which is based on a single 24-hour dietary recall.

## Background

### Healthy aging

Population aging is accelerating rapidly in Israel as well as worldwide, necessitating adaptation of the health care system and consideration of new approaches that serve the specific needs of older adults [1]. According to current forecasts, the percentage of persons 65 years and older will increase from 8.5% in 2015 to 19.0% by 2030 [2]. The concept of healthy aging is generally described as optimizing opportunities for improving and preserving health and physical, social, and mental wellness; and enhancing successful life-course transitions [3]. While this definition depicts healthy aging or successful aging as a complex process of adaptation to changes across the lifespan, the concept needs to be looked at in terms of a measurable outcome that can be empirically validated [4]. Despite the differences in healthy aging definitions, there is some consensus in the studies that 'successful ager' outcome should measure function in domains of cognitive, physical and mental well-being [4]. In our study, we intended to evaluate healthy aging using assessment of cognitive function and frailty, as described in the following sections.

## Frailty

Frailty is internationally recognized as an important medical syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems [5]. Frail older persons are at high risk of accelerated physical and cognitive functional decline, disability, and death [6]. The concept of frailty adopts an integrative approach which represents general properties of aging and health rather than particular functional deficiency or decline [7]. Assessment of frailty has implications both for the individual and on society at large, forecasting healthcare use [8 9] and providing opportunities for preventive intervention [10 11], thus making it a key issue in chronic disease management and healthy aging [12 13]. Based on 21 cohorts involving 61,500 participants, on average, 11% of community-dwelling subjects aged 65 years and older are defined as frail and another 42% as prefrail [14]. Nevertheless, the reported prevalence differed substantially, ranging from 4% to 59% due to different definitions and measurements of frailty status. Methods to measure frailty vary widely throughout the literature [15-18], with two principal models of frailty emerging: **(1)** The Fried and colleagues' *Biological Phenotype* [5] framework, which conceptualizes frailty as a biologic syndrome characterized by a decline in overall function and loss of resistance to stressors. This model is comprised of five physical indicators including low physical activity, weak grip strength, slow walking speed, exhaustion, and unintentional weight loss**. (2)** The Rockwood and colleagues' *Accumulation of Deficits* Index [19], which defines frailty as the cumulative effect of individual deficits. Under this model, frailty is measured by ~40 parameters of symptoms, signs, disease states and disabilities, collectively referred to as deficits. The index is a calculation of the presence or absence of each deficit as a proportion of total [8].

## Cognitive function

The field of aging and dementia is focusing on the characterization of the earliest stages of cognitive impairment. Mild cognitive impairment (MCI) is a recently described syndrome that is currently thought of as a transition phase between healthy cognitive aging and dementia [20]. MCI is defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life [21]. The estimated prevalence of MCI in population-based studies ranges from 10% to 20% in people older than 65 years of age. Prevalence rates mostly vary as a result of different diagnostic criteria as well as different sampling and assessment procedures [22]. Clinical studies indicate that older adults with MCI will progress to Alzheimer's Disease (AD) at a rate of 10% to 15% per year, compared with healthy control subjects who convert at a rate of 1% to 2% per year [23], making it

an area of intense interest for theoretical and practical reasons. A widely recognized instrument for detection of cognitive impairment is the Mini-Mental State Examination (MMSE) [24 25]. The MMSE consists of thirty questions and has a maximum score of 30 points. MCI will be assessed according to poor performance on MMSE (i.e., a score of 1.5 standard deviations below the age- and education-specific mean). In addition, the key criteria that distinguish MCI from dementia are preservation of independence in functional abilities and lack of significant impairment in social or occupational functioning [25 26]. Cognitive decline definition among prospective studies vary [27] with a more commonly used method which define cognitive decline as the 10% of the sample who declined the most (i.e., the 90$^{th}$ percentile of decline). Such a population-based cutoff point has showed to be sensitive and specific indicator of cognitive decline [28] and has been used in different studies [29-32].

**Nutrition** Nutrition is an important element of health in the older population that affects and is affected by the aging process [33 34]. Malnutrition is highly prevalent among older adults and associated with a general decline in physical and mental functioning, higher hospitalization rate and increased mortality [33]. Eating patterns of various cultures around the world have been associated with risk for chronic diseases [35]. Accordingly, several countries have issued dietary recommendations aimed at chronic disease prevention [36]. However, little is known about the interactive effects of dietary behavior and diet quality on overall risk, as food and nutrients are not eaten in isolation. Consequently, indices of dietary quality, patterns, and variety are increasingly used by nutritional epidemiologists [37]. The Healthy Eating Index-2010 (HEI-2010) [38] is such an index, originally released in 1995 and then updated in 2010 by the US Department of Agriculture (USDA) as a measure of diet quality. The concept of nutritional deficiency as a determinant of frailty development is not new but whether it is a predictor or consequence of frailty has not been investigated adequately [39]. Several studies have shown that low intake of certain micronutrients and protein is associated with a higher risk of developing frailty. However, very few studies have assessed the effect of overall dietary patterns on frailty [40]. Two studies have suggested that increasing adherence to Mediterranean diet (MD, a diet characterized by high intake of fish, vegetables, legumes, fruits, cereals, and unsaturated fatty acids [41]) is associated with decreasing risk of frailty among community-dwelling older adults in Spain and Italy [42 43]. In addition, it was recently demonstrated that higher adherence to MD is associated with lower AD risk [44 45]. However, in most studies the MD score was defined from sample-specific scores; thus, only the relative but not the absolute effect of MD was assessed, and the results of these studies are difficult to compare across populations.

## Research Objective

### General objective

Investigate the relationship between dietary patterns and healthy aging as measured by cognitive function and frailty

### Specific aims

**A.** Develop a frailty index based on "Mabat Zahav" data (T0) and evaluate its prevalence and association with cause-specific mortality categories.

**B**. Assess development of frailty among study participants and examine its determinants, particularly dietary patterns.

**C**. Assess development of cognitive decline among current study participants and examine its determinants, particularly dietary patterns.

**D.** Investigate general long-term changes of dietary patterns, consumption and nutritional status among study participants.

### Research hypothesis

We hypothesize that diet quality in older adults is predictive of general well-being and a variety of clinical outcomes including frailty state and cognitive changes.

## Methods/Design

### Research design

The study employs a cohort study design. It constitutes the second interview (T1) of Mabat Zahav study [46]. The First National Health and Nutrition Survey of Older Adults Aged 65 and Over in Israel ("Mabat Zahav") was carried out in 2005-2006 by the Israel Center for Disease Control (ICDC) and the Nutrition Department of the Israel Ministry of Health. The data collected on the survey included information regarding health and nutrition status, health behaviors (physical activity, alcohol consumption, medication use, use of nutrition supplements), knowledge and attitudes regarding nutrition, and utilization of health services. The survey framework and population is further described in the following

section. The current study questionnaire (T1) duplicates most parts of the original (T0) interview (Fig. 1). In addition, measurements pertaining to frailty status and cognitive function are performed, as well as psychosocial assessments including the multidimensional scale of perceived social support (MSPSS) [47], geriatric depression scale (GDS) [48] and the short form of health-related-quality of life (SF-12) [49].The added psychosocial questionnaires are in order to enable a more comprehensive analysis of the concept of healthy aging and well-being. The HEI-2010, a measure of diet quality retrospectively assessed at T0, will serve as the exposure variable and be assessed prospectively at T1 in order to evaluate general changes in diet quality and composition. Frailty at T0 is retrospectively assessed through the Rockwood and colleagues' Deficit Index [19 50]. The index will be developed according to published criteria6 in order to identify frail participants at study entry. Frailty will be assessed prospectively at T1 by both the Deficit Index and the Fried and colleagues' Biological Phenotype framework [5]. Cognitive changes and MCI will be assessed prospectively. Follow-up of mortality, overall and across specific categories, will be conducted among T0 participants through linkage to the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers.

**"Mabat Zahav" survey – study population**

The Mabat Zahav survey population was a random sample of Israeli citizens age ≥ 65 years old. The survey included 1,852 community-dwelling participants (1,536 Jews and 316 Arabs) residing in Israel, who had lived in the country for at least one year in urban and rural settlements with more than 20,000 residents. Exclusion criteria included: significant cognitive reduction-MMSE<17, current hospitalization for more than six months, hospitalization in a psychiatric institution, and hospitalization in a long-term-care institution. Survey methods included a personal interview in the interviewees' homes or sheltered accommodation using a structured questionnaire. The sampling framework was provided by the two major health funds in Israel; Clalit Health Services, and Maccabi Health Services, which represent 86.3% of all older adults citizens in Israel. Lists of members from each of the two health funds were divided into population groups (Jews and Arabs) according to name and identity number. Sampling was carried out in two stages. First stage: 5,100 people were randomly sampled, with 4,250 from the Jewish list, and 850 from the Arab list. Interviewing of individuals from the first sample begun in July 2005. Second stage: An additional sample was drawn in January 2006, of 4,250 Jews and 2,500 Arabs, since all lists with names selected in the first sample had been exhausted at that stage by interviewers working in the selected areas. The overall response rate among successful contacts, for both stages, was 29.1% in the Jewish sector and 35.4% in the Arab sector. Oversampling was carried out in the Arab population,

because of the small percentage of elderly in the Arab population (6.3%), in order to ensure a sample large enough to carry out statistical analyses and comparisons with the Jewish sector.
The interviews were held in multiple languages, and the questionnaires were translated accordingly: 1277 (69%) interviews took place in Hebrew, 316 (17%) in Arabic, 257 (14%) in Russian and 2 in English. The data collected on the survey included information regarding health and nutrition status, health behaviors (physical activity, alcohol consumption, medication use, use of nutrition supplements), knowledge and attitudes regarding nutrition, and utilization of health services among this population [46]. All data collected from 1,799 subjects are available online at the ministry of health government web site [51].

**Exclusion criterion in current research stage (T1):**

Significant cognitive reduction as measured by a MMSE score of less than 17 [24 52] or inability to communicate.

**Sample size**

Among T0 initial participants (1,852), 1,799 (1,499 Jews and 300 Arabs) questionnaires were included in the final survey analysis. Forty-six participants (29 Jews and 17 Arabs) had a MMSE score of less than 17 (after adjustment for age and education), and seven questionnaires were only partially completed and therefore excluded from the statistical analysis. According to the mortality registry of the Ministry of Health, 1,115 participants were alive in February 2017. We assume that 25% of candidates will be unable to participate due to either exclusion criteria or severe medical condition and another 20% could not be contacted due to address or telephone number changes. We expect a response rate of 55%-60% among the remaining candidates for T1 interview, and so about 600 subjects are expected to be re-interviewed (Fig.2). Our efforts to maximize recruitment include the following steps:
Disconnected phone numbers and no response: **a.** Locating address changes via the Ministry of Interior database. **b.** Searching by the Israeli non-commercial telephone directory according to city of residence and family name only (in case of incorrect street name). **c.** Conducting ten attempts to contact each non-response.
Refusal: We are trying to encourage cooperation by **a.** Offering to conduct interviews 7 days a week, morning times and afternoons. **b.** Offering to divide the interview into two separate times, in case the length of the interview is a concern for the participant. **c.** Request to try re-appeal in a few weeks or month.

**Data collection** A personal interview is conducted in the interviewees' homes by trained interviewers using a structured questionnaire. Anthropometric measurements are performed using standardized protocols. Interviews are conducted in Hebrew, Arabic or Russian. Estimated time of an interview is an hour and a half. In case the participant is unable to complete the questionnaire by himself/herself, but still meets inclusion criteria, information from a proxy is obtained regarding dietary intake, chronic diseases and co-morbidities, activities of daily living (ADL), sociodemographic status and medication use. The proxy interview does not include the following assessments: GDS, SF-12, MSPSS and self-rated health. All data (except the 24-hour dietary recall) are collected using KoBotoolbox [53] software which is a freely available application to design surveys for data collection through smart devices and run on Android based platforms. The data are exported into a password protected Excel file on a daily basis. All responses are typed directly during the interview through Lenovo TAB2 A10-30 tablet. The 24-hour dietary recall is handwritten before being typed to "Tzamert" program [54], an Israeli nutrient data program, which enables recording of food intake and calculation of nutrient intake. In case of any technical difficulties, the questionnaire is completed manually by the interviewer. A pilot study (n=30) was conducted, after which questionnaires, research tools, and protocol were finalized.

Exposure variable: The HEI-2010 score at baseline (T0): Dietary data from the 24-hour dietary recall questionnaire was entered into the "Tzamert" program. The program uses the nutrient data in the BINAT program- the Israeli nutrient database which is maintained and updated by the Nutrition Department of the Ministry of Health. An HEI-2010 score [37 55] will be calculated for T0 and T1 interviews separately. The HEI-2010 has twelve components, nine of which assess adequacy of the diet, including 1) total fruit; 2) whole fruit; 3) total vegetables; 4) greens and beans; 5) whole grains; 6) dairy; 7) total protein foods; 8) seafood and plant proteins; and 9) fatty acids. The remaining three: refined grains, sodium, and empty calories assess dietary components that should be consumed in moderation. For each component, the respondents receive a minimum score of 0 and a maximum score of 5 or 10 (for perfect adherence to recommendations); intermediate degrees of adherence are calculated proportionately. Thus, the overall index has a range from 0 (worst) to 100 [37 55].

Nutritional status assessments:

(1) Dietary recall: The multiple-pass 24-hour dietary recall questionnaire is administrated**.** The method was originally developed by the USDA in order to limit the extent of underreporting that occurs with self-reported food intake [56]. The interviewer uses three distinct passes to gather information about a subject's food intake during the preceding 24 hours. The first pass is termed the *quick list*; here the interviewees are asked to recall all they had eaten and drunk in the 24-hour period that preceded the interview. The second pass is termed the *detailed description*. In this pass, the interviewees are asked to clarify any foods mentioned in the quick list. The third pass is termed the *review*. The interviewer reviews the list of foods mentioned and probes for additional eating occasions and clarifies food portion sizes [56]. In order to assist the interviewees in identifying food types and quantities during the interview, the interviewers use the "Food and Food Quantities Guide" which is partially based on the Food Guide of the USDA. The guide includes detailed questions on foods, as well as many photographs of Israeli foods. In order to facilitate quantification of amounts consumed, the interviewers use, in addition to the guide, identification aids such as a measuring cup, tablespoon, and teaspoon.

(2) Food security: Household food security is defined as a situation whereby all household members have access at all times to a food supply which is adequate for a healthy active life. Food security is assessed using the short 6-item food security USDA questionnaire [57].

(3) Malnutrition risk: Modified Mini Nutritional Assessment-Short Form (MNA-SF) [58]. The 6-item questionnaire is a nutritional screening tool that assesses malnutrition risk.

Outcome variables:

Frailty assessment: Frailty at T0 and T1 is assessed by the *Deficit Index* model [19 50]. Under this model, frailty is measured by ~40 parameters of symptoms, signs, disease states and disabilities, collectively referred to as deficits. Adapting the Rockwood index of accumulation of deficits method [7] with T0 data, a Frailty Index (FI) was developed comprising 33 variables. The FI at T1 will comprise the same variables as T0 FI and will serve as the outcome measure. The FI is a calculation of the presence or absence of each deficit as a proportion of the total. Dichotomous items are coded as 0 if the deficit is absent and as 1 if it is present, while ordinal variables are graded into a score between 0 and 1 (0 representing no impairment, 0.5 for minor impairment, and 1 for major impairment). Scores are then summed up and divided by the total number of variables, yielding a frailty index between 0 and 1, with 1 representing the greatest frailty (a threshold of ≥0.25 is typically used to define frailty) [59]. Frailty at T1

is additionally assessed by the *Biological Phenotype* model [60]. Frailty using this instrument is identified by the presence of three or more of the following components: 1. Shrinking: weight loss, unintentional, of more than 4.5 Kg, or more than 5% of body weight, in the previous year; 2. Weakness: grip strength in the lowest 20% (adjusted for sex and body mass index); 3. Poor endurance and energy: as indicated by self-report of exhaustion; 4. Slowness: the slowest 20% of the participants in the sample, based on time of a 5-meter walk (adjusted for sex and standing height); 5. Low physical activity level: a weighted score of kilocalories expended per week will be calculated based on a Physical Activity Scale for the Elderly (PASE) questionnaire [61]. The lowest quintile of physical activity will be identified for each gender.

Cognitive assessment**:** Cognitive status is evaluated using the MMSE [24] the maximum score is 30. The questions typically have been grouped into seven categories, each representing a different cognitive domain or function: orientation to time (5 points); orientation to place (5 points); registration of three words (3 points); attention and calculation (5 points); recall of three words (3 points); language (8 points) and visual construction (1 point) [62]. The MMSE scores will be education- and age-standardized [63]. Some participants cannot complete test items due to physical disability. Items that the participant cannot complete will not be included in the total score. The MMSE will be scored out of the items that can be tested [64]. Cognitive impairment will be defined as a score < 24 [24].Cognitive decline will be calculated as the MMSE score difference between 2005 and 2017and will be defined by the 10% of the sample who declined the most (i.e., the 90$^{th}$ percentile of decline) MCI will be assessed according to poor performance on MMSE (i.e., scored 1.5 standard deviations below the age- and education-specific mean) and preserved functional independence according to Katz et al. scale of activities of daily living (ADL) score [25 26]. Both cognitive decline and MCI will serve as outcome measurements and separately be investigated in relation to dietary quality.

Other covariates:

Health status evaluation: The questionnaire includes data on self-rated health (current status and recent trajectories), chronic diseases and co-morbidities (e.g., cardiovascular diseases, Parkinson's disease, respiratory diseases, renal disease, cancer, glaucoma and cataract, diabetes mellitus, osteoporosis, hypertension). In addition, the questionnaire includes demographic details, alcohol consumption, and smoking habits information.

Assessment of disabilities: Function is assessed by the Katz scale of Activities of Daily Living [65] based on ability to dress, shower/bathe, sit down and rise from a chair, eat and go to the bathroom. The maximum score is 15, with a score of 5 indicating "no functional limitations," a score of 6-10 indicating some functional limitations, and a score of 11 or more indicating several functional limitations.

Psychosocial assessments: Assessments include depression, perceived social support and health-related quality of life (SF-12). Depression is evaluated via a 5-item short form of the Yesavage geriatric depression scale (GDS) [48]. A score of 2 or higher indicates possible depression. Social support is assessed through the Multidimensional Scale of Perceived Social Support (MSPSS) [66], a 12-item questionnaire designed to measure perceptions of support from three sources: family, friends and a significant other (4 items for each source). Answers are given on a 1-7 scale. Weighted scores are calculated by averaging the specific items, each scale (source) individually and the entire questionnaire. A high score represents a high level of perceived social support. Health-related quality of life is evaluated via a short form of a multidimensional measure of health-related quality of life SF-12 [49], physical (PCS) and mental (MCS) component scores will be constructed from SF-12, using standard (U.S.) and country-specific scoring algorithms.

Drugs: The participants are asked about any medication use on a regular basis (prescription as well as over-the-counter drugs). In the preliminary letter, the participants are asked to prepare their regular medication list. Medications are coded using the ATC (Anatomical Therapeutical and Chemical) system, developed by the World Health Organization (WHO) [46].

Anthropometric measurements: Include standing height and weight, ulna length (to calculate height, using recognized formulae), waist and mid-upper arm circumference. Weight measurements are carried out using an analog scale suitable for weighing up to 130 kg, with accuracy to 0.5 kg. The scales are placed on an uncarpeted floor and calibrated before weighing. Height is measured using a spring coil measuring tape. Waist circumference is measured using a flexible tape, with the ability to measure up to 150 cm, at the narrowest part of the torso, where a "fold" is created when bending sideways [46]. Mid-upper arm circumference is measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromion) using a flexible tape [67].

Blood pressure and pulse measurements: The interviewers are conducting blood pressure and pulse measurements using an electronic monitor. The measurements are carried out according to a protocol based on recommendations of the American Heart Association [68]. Sitting blood pressure and pulse are measured in the right arm and is carried out twice, with a minute rest in-between. In case of a difference of 10% or more between measurements of either systolic or diastolic pressure, a third measurement is carried out. The final value will be the mean of measurements.

Mortailty and cause of death: Original participants were linked to the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers. Mortality information is managed by the Ministry of Health. Since 1999, deaths are coded according to the International Classification of Diseases, Tenth Edition (ICD-10). Cause-specific mortality categories were divided into cardiovascular disease (CVD) deaths and non-CVD deaths. According to the classification used by the American Heart Association [69], CVD deaths are divided into three categories: coronary heart disease (CHD), diseases of the heart and diseases of the circulatory system (ICD-10: I00-I99).



**Quality assurance**

Quality assurance is carried out in various ways: (1) A pilot study (n=30) was conducted, after which questionnaires and research tools were finalized; (2) Interviewer training: A 2-day seminar were designed and included standard procedures of administrating research questionnaires, performing anthropometric measurements and handling data in general; (3) All interviews (under interviewee consent) are recorded; (4) The study coordinator randomly monitor 5-10% of all interviews; (5) Interim data analysis will include division per each interviewer in order to assess potential bias; (6) Dietary data quality assurance includes: ***a.*** a food recall check: time sequence, completeness of information, matching of the items in the "Quick List" with those in the "Comprehensive List", and ***b***. following data entry into the Tzamert program, testing will be performed for outliers, in appropriate quantities, lack of correlation between meal times and types, and missing quantities and incorrect coding.

**Statistical analysis according to specific aims**

Analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC), IBM SPSS version 25 (SPSS, Chicago, IL) and R version 3.2.3 (R Development Core Team).

**A.** Frailty categories assessed at baseline (T0; frail vs. robust) will serve as the exposure variable. Baseline characteristics across frailty index categories will be compared by chi-squared test for categorical variables and student-t-test for continuous variables. Cox proportional hazards regression models [70] will be fitted to evaluate the hazard ratios for death and other time-to-event outcomes associated with baseline exposure groups. Several adjustment methods will be applied including traditional multivariable adjustment and propensity score adjustment [71]. The incremental discriminatory ability of frailty index over demographic and SES variables in predicting death during a 12-year follow up will be evaluated by the c-statistic. Assessing the c-statistic and its corresponding standard error from Cox proportional hazards models will be performed with methods proposed by Harrell et al. [72].

**B.** Frailty among current study participants (T1) will be assessed by two methods, and Weighted Kappa will be used to assess the agreement in the results of the two methods that measure frailty [73]. Baseline characteristics across HEI categories as measured at T0 will be compared by chi-squared test for categorical variables and analysis of variance for continuous variables. The predictive role of nutritional indices in the long-term incidence of frailty will be assessed using multivariable logistic regressions models [74]. Frailty status, assessed at follow-up (T1), will be treated as a dichotomous outcome (frail vs. robust). Adjustment will be made for sociodemographic, clinical, and psychosocial variables, via either multivariable adjustment or propensity score [75]. We will exclude participants who were frail at baseline. Of the 1,799 participants in the original survey, many are no longer able to participate in T1 interview (death, loss to follow-up, non-response). Because frailty status could not be assessed among the latter group, selection bias is introduced [76]. This bias will be addressed through an adaptation of a marginal structural model, applying inverse probability weights [76 77]. Accordingly, the probability of original participants to take part in the second interview will be estimated. Each observation will then be weighted by the reciprocal (i.e., the inverse) of the predicted probability of participating at T1.

**C.** In order to investigate dietary patterns and their potential role in longitudinal cognitive changes, we will consider several methods for defining cognitive decline as they vary considerably [27] and compare results using different definitions. We will exclude participants with cognitive impairment at baseline (MMSE score < 24). The predictive role of nutritional indices in cognitive changes will

be assessed using generalized linear model [78] or logistic regression models [74] depending on the cognitive decline definition method used. Several adjustment methods will be applied including multivariable adjustment or propensity score [75]. Selection bias will be addressed through an adaptation of a marginal structural model, applying inverse probability weights [76 77] as described above.

**D.** Descriptive statistics of dietary consumption and nutritional status among current study participants (T1) will include assessing adequate macro and micronutrients consumption on the basis of Dietary Reference Intake (DRI) [79 80] and the prevalence of malnutrition risk. Results will be expressed as means and standard deviation (SD) or percentages as appropriate. In order to investigate different characteristics of longitudinal changes in diet quality among participants with two dietary recall assessments, we will calculate the difference between HEI scores for each participant and divide them into different categories from the largest decrease to the largest increase. Initial lifestyle characteristics and changes in these characteristics according to the category of change in the HEI score will be calculated.

**Approach to missing data**

Missing values for the variables comprising the frailty index will be imputed using multiple imputation methodology [81]. The number of complete (imputed) datasets will be defined by the following formula: $(1+\lambda/m)^{-1}$= *efficiency*, where λ is the fraction of missing information and *m* the number of datasets to impute. We will assume an efficiency of 0.975. Missing values will be replaced by imputed values based on models incorporating demographic, socioeconomic, psychosocial, and clinical variables. The results of these datasets will then be combined using Rubin's rules [81].

**Estimated statistical power**

Among 1,800 initial participants, some 1,115 survived so far. About 600 subjects are expected to be re-interviewed, assuming a response rate of 55% for T1 interview. Considering frailty prevalence of over 35% at the estimated average age of 84 years in T1 interview[82], about 250 frail subjects can be expected. This sample size is sufficient for detecting an adjusted odds ratio for frailty of ≤ 0.60 between the upper vs. lower HEI score tertiles (significance level at 5% and power of 80%). A previous study showed after a 6-year follow-up that higher adherence to MD diet was associated with lower odds of developing frailty [OR = 0.30 (95% CI: 0.14, 0.66)] [43].

**Patient and Public Involvement**

Patients and or public were not involved.

**Ethical aspect**

Ethical approval for the study was obtained from the Helsinki Committee of Chaim Sheba Medical Center at Tel Hashomer and the Ethical Committee of Tel-Aviv University. Potential participants receive a preliminary letter with a description of the study, a request to participate and an announcement that telephone contact would be made in the near future. In addition, the letter provides the telephone number of the research coordinator for further questions. After a minimum of two weeks, potential participants are contacted by telephone in order to set an interview appointment for those who agree to participate. The interview does not involve clinical procedures, and no human biological specimens are collected. Therefore, participants' burden is minimal. Each interviewee is asked to sign an informed consent form.

**Dissemination**

The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

## Discussion

The ILSA sets out to transform a large national survey of older adults with a broad-spectrum data into a cohort study with a specific age-related questionnaire including comprehensive geriatric assessment, evaluation of general health and quality of life. Obtaining data at two points in time, more than a decade apart, will allow us to evaluate long-term changes in older adults population and examine dietary role in the context of healthy aging and adverse clinical outcomes. Participants' estimated current mean age of 84 years old, defined as the "oldest-old" have over past decades been the most rapidly expanding segment of the population in developed countries and also the most susceptible to disease and disability [83]. Only few studies have explicitly examined the concept of robust aging among the oldest-old and investigated its heterogeneity in functioning, cognitive abilities, diet quality, and nutritional status changes. Both frailty and cognitive decline are at the core definition of healthy aging and are highly prevalent in older people; still, as their status varies considerably among older adults, important issues

such as how they develop, are they preventable, and can they be detected reliably have yet to be defined. Our study design has several limitations. Of the 1,799 participants in the original survey, many are no longer able to participate in T1 interview (death, loss to follow-up, non-response). Because frailty status and cognitive state could not be assessed among the latter group, selection bias is introduced. This bias will be addressed through applying inverse probability weights based on estimated propensity score. Another limitation is the fact that dietary quality assessment (exposure variable) is based on a single 24-hour dietary recall; although evaluation of the HEI score is suitable for a single 24-hour dietary recall intake [84 85], individual diets can vary greatly from day to day. Furthermore, we cannot preclude that participants may have changed their dietary habits during the follow-up. The 24-hour dietary recall tool is wildy used to assess dietary intake in population studies since 1965 [86], with studies indicating its accuracy for estimating energy intake [56 87]. In addition, the multiple-pass 24-hour dietary recall technique, which is used in our study, mange to limit the extent of underreporting that occurs with single self-reported food intake [56 88]. Like most similar studies, self-report information and information form a proxy can lead to misclassification bias that may lead to under or overestimation of dietary recall, frailty and other outcomes. Nevertheless, examining the role of nutritional dietary pattern in the context of healthy aging and adverse clinical outcomes may help to broaden our knowledge regarding the older adults population, provide a scientific basis on which policymakers can rely and pave the way for early therapeutic interventions.

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**Figure legends:**

Figure 1: Study design sketch. [1]Mini Mental State Examination; [2]General Health Questionnaire; [3]Activities of Daily Living; [4]Mini Nutritional Assessment-Short Form; [5]Healthy Eating Index; [6]Geriatric Depression Scale; [7]Short Form of health-related-quality of life.

Figure 2: Sample size flow chart.

## Footnotes

### Authors' contributions

AG, study coordinator of the ILSA, drafted the manuscript, assisted in the conception of the study and led field activities and study monitoring; UG, co-investigator for the ILSA, conceived of the study concept and design and supervised the study; T Shohat, co-investigator of the ILSA and physician-in-charge of the study; LKB, principal investigator of MABAT ZAHAV survey; T Shimony, coordinator of MABAT ZAHAV survey; YG, principal investigator of the ILSA, conceived of the study concept and design and co-drafted the manuscript. All authors revised, reviewed and approved the final paper.

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### Competing interests

The authors declare that they have no competing interests.

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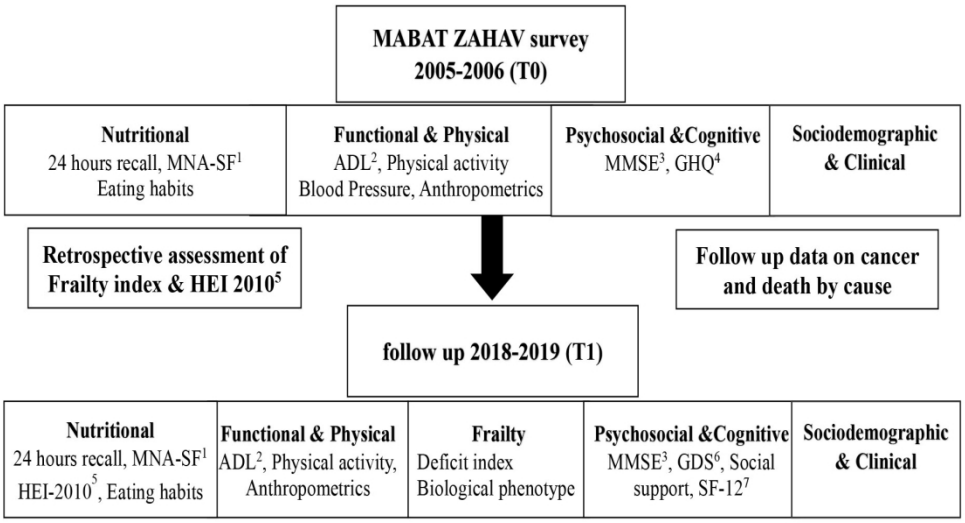


Figure 1: Research design sketch.[1]Mini Mental State Examination; [2]General Health Questionnaire; [3]Activities of Daily Living; [4]Mini Nutritional Assessment– Short Form; [5]Healthy Eating Index; [6]Geriatric Depression Scale; [7]Short Form of health-related-quality of life.

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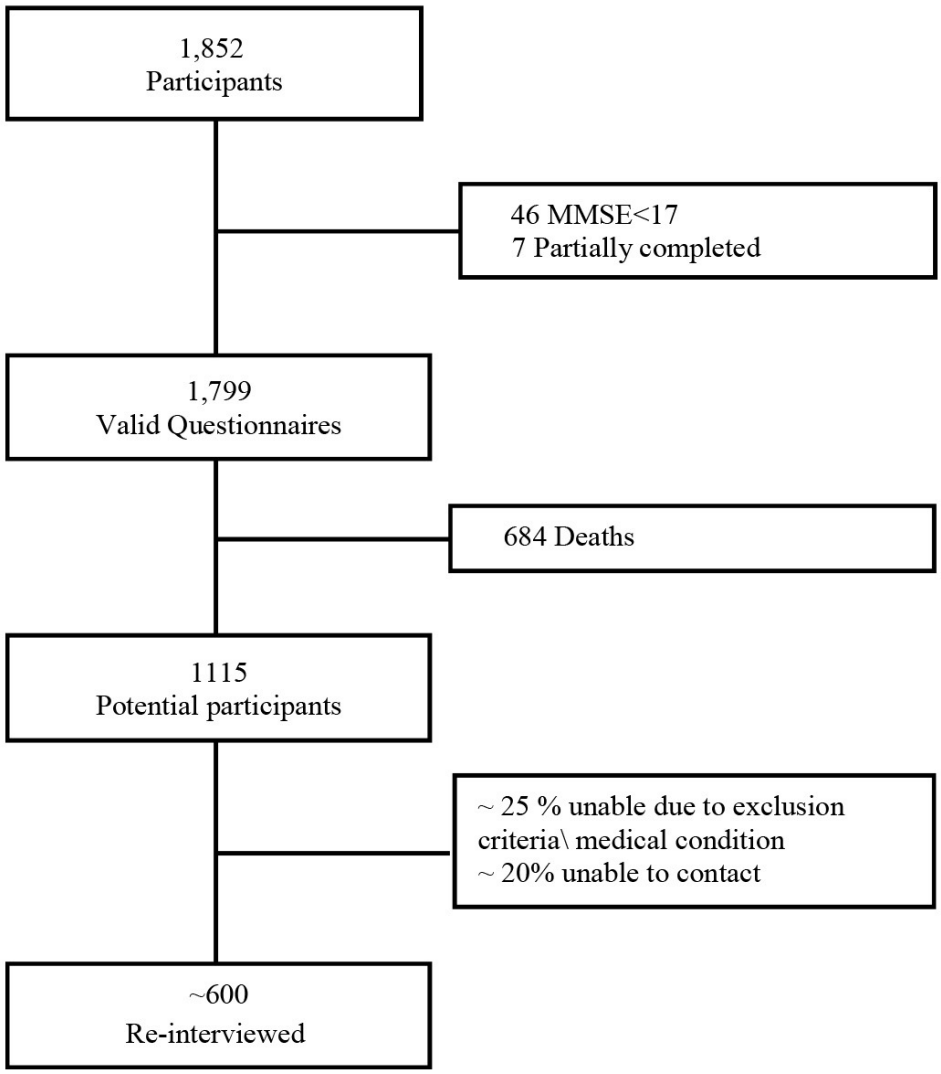


Figure 2. Sample size flow chart.

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# Diet Quality in Relation to Healthy Aging. The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

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# Diet Quality in Relation to Healthy Aging.

## The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

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Diet Quality in Relation to Healthy Aging.

# The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

Introduction: Population aging is accelerating rapidly in Israel as well as worldwide, necessitating adaptation of the health care system and consideration of new approaches that serve the specific needs of older adults. In addition to cognitive function, frailty is one of the most challenging expressions of physical and mental aging, a multidimensional syndrome of increased vulnerability. Several studies have shown that low intake of certain micronutrients and protein is associated with higher risk of frailty and cognitive impairment. However, whether global diet quality is involved in the etiology of the latter outcomes is unclear.

Methods and analysis: We are conducting, among older adult subjects who took part in "MABAT ZAHAV" (Israeli National Health and Nutrition Survey of Older Adults) in 2005-2006 (T0, N=1,852) an extensive follow-up interview (T1) that includes comprehensive geriatric assessment and evaluation of general health and quality of life. Diet quality is evaluated using the Healthy Eating Index (HEI) 2010, based on 24-hour diet recall measured at T0 and T1. Frailty is assessed using two different approaches: the phenotype framework and the accumulation of deficits model. Cognitive function is assessed by Mini Mental State Examination (MMSE) and cognitive decline by the difference between repeated MMSE measurements. Different analytic methods will be applied to evaluate the role of diet quality in development of frailty and cognitive decline with inverse probability weighting used to minimize attrition bias. About 600 subjects are expected to be interviewed between May 2017 and December 2019.

Ethics and dissemination: Ethical approval was obtained from the Helsinki Committee of Sheba Medical Center, Tel Hashomer, Israel and the Ethical Committee of Tel-Aviv University. All participants sign an informed consent form. The findings of the study will be published in peer-reviewed journals.

Keywords: diet quality; epidemiology; older adults; healthy aging; longitudinal studies

## Strengths and limitations of this study

- The study transforms a large national survey of older adults with a broad-spectrum data into a cohort study with a specific age-related questionnaire including comprehensive geriatric assessment.
- Obtaining data at two points in time, more than a decade apart, will allow us to evaluate long-term changes in older adult population and examine adverse clinical outcomes.
- Selection bias due to death, loss to follow-up and non-response.
- Misclassification bias due to self-report data and nutritional assessment which is based on a single 24-hour dietary recall.

## Background

### Healthy aging

Population aging is accelerating rapidly in Israel as well as worldwide, necessitating adaptation of the health care systems and consideration of new approaches that serve the specific needs of older adults [1]. According to current forecasts, the percentage of persons 65 years and older will increase from 8.5% in 2015 to 19.0% by 2030 [2]. The concept of healthy aging is generally described as optimizing opportunities for improving and preserving health and physical, social, and mental health; and enhancing successful life-course transitions [3]. While this definition depicts healthy aging (also termed successful aging) as a complex process of adaptation to changes across the lifespan, the concept needs to be looked at in terms of a measurable outcome that can be empirically validated [4]. Despite the differences in healthy aging definitions, there is some consensus in the studies that 'successful ager' outcome should measure function in domains of cognitive, physical and mental well-being [4]. In our study, we intend to transform a large national survey of older adults into a cohort study with specific age-related questionnaires including general health, functional status, quality of life, social support, depression and cognitive function. Healthy aging is assessed by various scientifically recognized measures, with emphasis on frailty state and cognitive function. The predictive role of diet quality in the devlopment of the latter outcomes will be evaluted, as described in detail in the following sections.

### Frailty

Frailty is recognized as an important medical syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems [5]. Frail older persons are at high risk of accelerated physical and cognitive functional decline, disability, and death [6]. The concept of frailty adopts an integrative approach which represents general properties of aging and health rather than particular functional deficiency or decline [7].

Assessment of frailty has implications both for the individual and on society at large, forecasting healthcare use [8 9] and providing opportunities for preventive intervention [10 11], thus making it a key issue in chronic disease management and healthy aging [12 13].

Methods to measure frailty vary throughout the literature [14-17], with two principal models of frailty emerging: **(1)** The Fried and colleagues' *Biological Phenotype* [5] framework, which conceptualizes frailty as a biologic syndrome characterized by a decline in overall function and loss of resistance to stressors. This model is comprised of five physical indicators including low physical activity, weak grip strength, slow walking speed, exhaustion, and unintentional weight loss**. (2)** The Rockwood and colleagues' *Accumulation of Deficits* Index [18], which defines frailty as the cumulative effect of individual deficits. Under this model, frailty is measured by ~40 parameters of disease states, functional status, cognitive function, and psychosocial status, collectively referred to as deficits. The index is a calculation of the presence or absence of each deficit as a proportion of total [8]. Frailty and successful aging models share common aspects of aging [19]. Frailty is recognized as an independent determinant of successful aging, supporting the idea that successful agers might be nonfrail individuals [19 20].

**Cognitive function**

Another important aspect of successful aging is the maintenance of cognitive function [21]. Cognitive function is a predictor of independence and quality of life [22]. Cognitive function assessed repeatedly is important because it is possible for an elderly person to have a normal cognitive score that still represents a significant decline for that individual. Mild cognitive impairment (MCI) is a syndrome that is currently thought of as a transition phase between healthy cognitive aging and dementia [23]. MCI is defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with Activities of Daily Life (ADL) [24]. The estimated prevalence of MCI in population-based studies ranges from 10% to 20% in people older than 65 years of age. Clinical studies indicate that older adults with MCI will progress to Alzheimer's Disease (AD) at a rate of 10% to 15% per year, compared with healthy control subjects who convert at a rate of 1% to 2% per year [25], making it an area of intense interest for theoretical and practical reasons. A widely recognized instrument for detection of cognitive impairment is the Mini-Mental State Examination

(MMSE) [26 27]. The MMSE consists of thirty questions and has a maximum score of 30 points. MCI will be assessed according to poor performance on MMSE (i.e., a score of 1.5 standard deviations below the age- and education-specific mean) and presereved independence in functional abilities [27 28].

**Nutrition**

Nutrition is an important element that affects and is affected by the aging process [29 30]. Malnutrition is highly prevalent among older adults and associated with a general decline in physical and mental functioning, higher hospitalization rate and increased mortality [29]. Eating patterns of various cultures around the world have been associated with risk for chronic diseases [31]. However, examining the intake of a single nutrient or food group does not account for the complexity of dietary intake, as food and nutrients are not eaten in isolation. Consequently, indices of dietary quality, patterns, and variety are increasingly used by nutritional epidemiologists [32]. The Healthy Eating Index-2010 (HEI-2010) [33] is such an index, originally released in 1995 and then updated in 2010 by the US Department of Agriculture (USDA) as a measure of diet quality. The concept of diet quality as a determinant of frailty development is not new but whether it is a predictor or consequence of frailty has not been investigated adequately [34]. Several studies have shown that low intake of certain micronutrients and protein is associated with a higher risk of developing frailty. However, very few studies have assessed the effect of overall diet quality on frailty [35]. Two studies have suggested that increasing adherence to Mediterranean diet (MD, a diet characterized by high intake of fish, vegetables, legumes, fruits, cereals, and unsaturated fatty acids [36]) is associated with decreasing risk of frailty among community-dwelling older adults in Spain and Italy [37 38]. In addition, it was recently demonstrated that higher adherence to MD is associated with lower AD risk [39 40]. However, in most studies the MD score was defined from sample-specific scores; thus, only the relative but not the absolute effect of MD was assessed, and the results of these studies are difficult to compare across populations.

## Research Objective

### General objective

Investigate the relationship between diet quality and healthy aging as assessed by scientifically recognized measures.

### Specific aims

**A.** Develop a frailty index based on "Mabat Zahav" data (T0) and evaluate its prevalence and association with subsequent survival.

**B**. Examine the predictive role of diet quality in development of frailty, cognitive changes and other healthy aging aspects among study participants.

**C.** Investigate long-term changes of dietary consumption and nutritional status among study participants.

### Hypothesis

We hypothesize that frailty will be associated with survival and that diet quality in older adults is predictive of successful aging as measured by a variety of clinical outcomes.

## Methods/Design

### Research design

The study employs a cohort study design. It constitutes the second interview of Mabat Zahav study [41]. The First National Health and Nutrition Survey of Older Adults Aged 65 and Over in Israel ("Mabat Zahav") was carried out in 2005-2006 by the Israel Center for Disease Control (ICDC) and the Nutrition Department of the Israel Ministry of Health. The data collected on the survey included information regarding health and nutrition status, health behaviors (physical activity, alcohol consumption, medication use, use of nutrition supplements), knowledge and attitudes regarding nutrition, and utilization of health services. The survey framework and population is further described in the following section. The current study questionnaire (T1) duplicates most parts of the original (T0) interview (Fig. 1). In addition, measurements pertaining to frailty status and cognitive function are performed, as well as psychosocial assessments including the multidimensional scale of perceived social support (MSPSS) [42], geriatric depression scale (GDS) [43] and the short form of health-related-quality of life (SF-12) [44].The added psychosocial questionnaires are in order to enable a more comprehensive analysis of the concept of healthy aging and well-being. The HEI-2010, a measure of diet quality retrospectively assessed at T0, will serve as the exposure variable and be assessed prospectively at T1 in order to evaluate general changes in diet quality and composition.

Frailty at T0 is retrospectively assessed through the Rockwood and colleagues' Deficit Index [18 45]. The index will be developed according to published criteria in order to identify frail participants at study entry. Frailty will be assessed prospectively at T1 by both the Deficit Index and the Fried and colleagues' Biological Phenotype framework [5]. Cognitive changes and MCI will be assessed prospectively. Mortality follow up will be conducted among T0 participants through linkage to the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers.

**"Mabat Zahav" survey – study population**

The Mabat Zahav survey population was a random sample of Israeli citizens age ≥ 65 years old. The survey included 1,852 community-dwelling participants (1,536 Jews and 316 Arabs) residing in Israel, who had lived in the country for at least one year in urban and rural settlements with more than 20,000 residents. Exclusion criteria of Mabat Zahav survey included: significant cognitive reduction (MMSE<17) and hospitalization at the time of the study. Survey methods included a personal interview in the interviewees' homes or sheltered accommodation using a structured questionnaire.

Sampling frame: Adults aged 65 and over insured by the two major HMO in Israel, Clalit Health Services and Maccabi Health Services, representing 86.3% of all of the elderly in Israel, were sampled. Oversampling was carried out in the Arab population, because of the small percentage of elderly in the Arab population (6.3%), in order to ensure a sample large enough for statistical analyses and comparisons with the Jewish sector. The overall sample size target was 1,800 participants, 1,500 Jews, and 300 Arabs.

Sampling method: Lists of insured older adults from each of the two HMO were combined and divided into population groups (Jews and Arabs). Sampling was carried out in two stages due to low response rate at the first stage, in order to meet the sample size target. First stage: 5,100 people were randomly sampled, with 4,250 from the Jewish list and 850 from the Arab list. Interviewing of individuals from the first sample commenced in July 2005. A total of 1,081 individuals were interviewed, of which 1,051 questionnaires met inclusion criteria (909 Jews and 142 Arabs). Second stage: An additional sample was drawn in January 2006, including 4,250 Jews and 2,500 Arabs, since the initial lists were exhausted. A total of 771 individuals were interviewed, of which 748 questionnaires met inclusion criteria (590 Jews and 158 Arabs). The interviews were held in multiple languages, and the questionnaires were translated accordingly: 1277 (69%) in Hebrew, 316 (17%) in Arabic, 257 (14%) in Russian and 2 in English [41]. All data collected are available online at the ministry of health government web site [46].

**Exclusion criterion in current research stage (T1):**

Significant cognitive reduction as measured by a MMSE score of less than 17 [26 47] or inability to communicate.

**Sample size**

Among T0 initial participants (1,852), 1,799 (1,499 Jews and 300 Arabs) questionnaires were included in the final survey analysis. Forty-six participants (29 Jews and 17 Arabs) had a MMSE score of less than 17 (after adjustment for age and education), and seven questionnaires were only partially completed and therefore excluded from the statistical analysis. According to the mortality registry of the Ministry of Health, 1,115 participants were alive in February 2017. We assume that 25% of candidates will be unable to participate due to either exclusion criteria or severe medical condition and another 20% could not be contacted due to address or telephone number changes. We expect a response rate of 55%-60% among the remaining candidates for T1 interview, and so about 600 subjects are expected to be re-interviewed (Fig.2). Our efforts to maximize recruitment include the following steps:

Disconnected phone numbers and no response: **a.** Locating address changes via the Ministry of Interior database. **b.** Searching by the Israeli non-commercial telephone directory according to city of residence and family name only (in case of incorrect street name). **c.** Conducting ten attempts to contact each non-respondent.

Refusal: We are trying to encourage cooperation by **a.** Offering to conduct interviews 7 days a week, morning times and afternoons. **b.** Offering to divide the interview into two separate times, in case the length of the interview is a concern for the participant.

**Data collection**

A personal interview is conducted in the interviewees' homes by trained interviewers using a structured questionnaire. Anthropometric measurements are performed using standardized protocols as described in a subsequent section. Interviews are conducted in Hebrew, Arabic or Russian. Estimated time of an interview is an hour and a half. In case the participant is unable to complete the questionnaire by himself/herself, but still meets inclusion criteria, information from a proxy is obtained regarding dietary intake, chronic diseases, ADL, sociodemographic status and medication use. The proxy interview does not include the following assessments: GDS, SF-12, MSPSS and self-rated health. All data (except the 24-hour dietary recall) are collected using KoBotoolbox [48] software which is a freely available application to design surveys for data collection through smart devices

and run on Android based platforms. The data are exported into a password protected Excel file on a daily basis. All responses are typed directly during the interview through Lenovo TAB2 A10-30 tablet. The 24-hour dietary recall is handwritten before being typed to "Tzamert" program [49], an Israeli nutrient data program, which enables recording of food intake and calculation of nutrient intake. In case of any technical difficulties, the questionnaire is completed manually by the interviewer. A pilot study (n=30) was conducted, after which questionnaires undertook minor adjustments.

Exposure variable: The HEI-2010 score at baseline (T0): Dietary data from the 24-hour dietary recall questionnaire was entered into the "Tzamert" program. The program uses the nutrient data in the BINAT program- the Israeli nutrient database which is maintained and updated by the Nutrition Department of the Ministry of Health. An HEI-2010 score [32 50] will be calculated for T0 and T1 interviews separately. The HEI-2010 has twelve components, nine of which assess adequacy of the diet, including 1) total fruit; 2) whole fruit; 3) total vegetables; 4) greens and beans; 5) whole grains; 6) dairy; 7) total protein foods; 8) seafood and plant proteins; and 9) fatty acids. The remaining three: refined grains, sodium, and empty calories assess dietary components that should be consumed in moderation. For each component, the respondents receive a minimum score of 0 and a maximum score of 5 or 10 (for perfect adherence to recommendations); intermediate degrees of adherence are calculated proportionately. Thus, the overall index has a range from 0 (worst) to 100 [32 50].

Nutritional status assessments:

(1) Dietary recall: The multiple-pass 24-hour dietary recall questionnaire is administrated**.** The method was originally developed by the USDA in order to limit the extent of underreporting that occurs with self-reported food intake [51]. The interviewer uses three distinct passes to gather information about a subject's food intake during the preceding 24 hours. The first pass is termed the *quick list*; here the interviewees are asked to recall all they had eaten and drunk in the 24-hour period that preceded the interview. The second pass is termed the *detailed description*. In this pass, the interviewees are asked to clarify any foods mentioned in the quick list. The third pass is termed the *review*. The interviewer reviews the list of foods mentioned and probes for additional eating occasions and clarifies food portion sizes [51]. In order to assist the interviewees in identifying food types and quantities during the interview, the interviewers use the "Food and Food Quantities Guide" which is partially based on the Food Guide of the USDA. The guide includes detailed questions on foods, as well as many photographs of Israeli foods. In order to

facilitate quantification of amounts consumed, the interviewers use, in addition to the guide, identification aids such as a measuring cup, tablespoon, and teaspoon.

(2) Food security: Household food security is defined as a situation whereby all household members have access at all times to a food supply which is adequate for a healthy active life. Food security is assessed using the short 6-item food security USDA questionnaire [52].

(3) Malnutrition risk: Modified Mini Nutritional Assessment-Short Form (MNA-SF) [53]. The 6-item questionnaire is a nutritional screening tool that assesses malnutrition risk.

Primary outcomes:

Frailty assessment: Frailty at T0 and T1 is assessed by the *Deficit Index* model [18 45]. Under this model, frailty is measured by ~40 parameters of symptoms, signs, disease states and disabilities, collectively referred to as deficits. Adapting the Rockwood index of accumulation of deficits method [7] with T0 data, a Frailty Index (FI) was developed comprising 33 variables. The FI at T1 will comprise the same variables as T0 FI and will serve as the outcome measure. The FI is a calculation of the presence or absence of each deficit as a proportion of the total. Dichotomous items are coded as 0 if the deficit is absent and as 1 if it is present, while ordinal variables are graded into a score between 0 and 1 (0 representing no impairment, 0.5 for minor impairment, and 1 for major impairment). Scores are then summed up and divided by the total number of variables, yielding a frailty index between 0 and 1, with 1 representing the greatest frailty (a threshold of ≥0.25 is typically used to define frailty) [54]. Frailty at T1 is additionally assessed by the *Biological Phenotype* model [5]. Frailty using this instrument is identified by the presence of three or more of the following components: 1. Shrinking: weight loss, unintentional, of more than 4.5 Kg, or more than 5% of body weight, in the previous year; 2. Weakness: grip strength in the lowest 20% (adjusted for sex and body mass index); 3. Poor endurance and energy: as indicated by self-report of exhaustion; 4. Slowness: the slowest 20% of the participants in the sample, based on time of a 5-meter walk (adjusted for sex and standing height); 5. Low physical activity level: a weighted score of kilocalories expended per week will be calculated based on a Physical Activity Scale for the Elderly (PASE) questionnaire [55]. The lowest quintile of physical activity will be identified for each gender.

Cognitive assessment**:** Cognitive status is evaluated using the MMSE [26]. The questions are grouped into seven categories, each representing a different cognitive domain or function: orientation to time (5 points); orientation to place (5 points); registration of three words (3 points); attention and calculation (5 points); recall of three words (3 points); language (8 points) and visual construction (1 point) [56]. The MMSE scores (maximum, 30 points) will be education- and age-standardized [47]. Some

participants cannot complete test items due to physical disability. The MMSE in these subjects will be scored out of the items that can be tested [57]. Cognitive impairment will be defined as a score < 24 [26]. Cognitive decline will be calculated as the MMSE score difference between 2005 and 2017 and will be defined by the 10% of the sample who declined the most (i.e., the 90$^{th}$ percentile of decline). MCI will be assessed according to poor performance on MMSE and preserved functional independence [28]. Poor performance on MMSE will be defined by a score of 1.5 standard deviations below the age- and education-specific mean. Preserved functional independence will be defined according to Katz et al. scale of ADL score [27 28].

Secondary outcomes:

Health status evaluation: The questionnaire includes data on self-rated health (current status and recent changes) and chronic diseases (e.g., cardiovascular diseases, Parkinson's disease, respiratory diseases, renal disease, cancer, glaucoma and cataract, diabetes mellitus, osteoporosis, hypertension). In addition, the questionnaire includes demographic details, alcohol consumption, and smoking habits information.

Assessment of disabilities: Function is assessed by the Katz scale of Activities of Daily Living [58] based on ability to dress, shower/bathe, sit down and rise from a chair, eat and go to the bathroom. The maximum score is 15, with a score of 5 indicating "no functional limitations," a score of 6-10 indicating some functional limitations, and a score of 11 or more indicating several functional limitations.

Psychosocial assessments: Assessments include depression, perceived social support and health-related quality of life. Depression is evaluated via a 5-item short form of the Yesavage GDS [43]. A score of 2 or higher indicates possible depression. Social support is assessed through the MSPSS [59], a 12-item questionnaire designed to measure perceptions of support from three sources: family, friends and a significant other (4 items for each source). Answers are given on a 1-7 scale. Weighted scores are calculated by averaging the specific items, each scale (source) individually and the entire questionnaire. A high score represents a high level of perceived social support. Health-related quality of life is evaluated via SF-12 [44], physical (PCS) and mental (MCS) component scores will be constructed from SF-12, using standard (U.S.) and country-specific scoring algorithms.

Drugs: The participants are asked about any medication use on a regular basis (prescription as well as over-the-counter drugs). In the preliminary letter, the participants are asked to prepare their

regular medication list. Medications are coded using the ATC (Anatomical Therapeutical and Chemical) system, developed by the World Health Organization (WHO) [41].

Anthropometric measurements: Include standing height and weight, ulna length (to calculate height, using recognized formulae), waist and mid-upper arm circumference. Weight measurements are carried out using an analog scale suitable for weighing up to 130 kg, with accuracy to 0.5 kg. The scales are placed on an uncarpeted floor and calibrated before weighing. Height is measured using a spring coil measuring tape. Waist circumference is measured using a flexible tape, with the ability to measure up to 150 cm, at the narrowest part of the torso, where a "fold" is created when bending sideways [41]. Mid-upper arm circumference is measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromion) using a flexible tape [60].

Blood pressure and pulse measurements: The interviewers conduct blood pressure and pulse measurements using an electronic monitor. The measurements are carried out according to a protocol based on recommendations of the American Heart Association [61]. Sitting blood pressure and pulse are measured in the right arm and is carried out twice, with a minute rest in-between. In case of a difference of 10% or more between measurements of either systolic or diastolic pressure, a third measurement is carried out. The final value will be the mean of measurements.

Mortality and cause of death: Original participants were linked to the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers. Mortality information is managed by the Ministry of Health. Since 1999, deaths are coded according to the International Classification of Diseases, Tenth Edition (ICD-10).

**Quality assurance**

Quality assurance is carried out in various ways: (1) A pilot study (n=30) was conducted, after which questionnaires and research tools were finalized; (2) Interviewer training: A 2-day seminar were designed and included standard procedures of administrating research questionnaires, performing anthropometric measurements and handling data in general; (3) All interviews (under interviewee consent) are recorded; (4) The study coordinator randomly monitor 5-10% of all interviews; (5) Dietary data quality assurance includes: ***a.*** a food recall check: time sequence, completeness of information, matching of the items in the "Quick List" with those in the "Comprehensive List", and ***b***. following data entry into the Tzamert program, testing will be performed for outliers, in

appropriate quantities, lack of correlation between meal times and types, and missing quantities and incorrect coding.

**Statistical analysis according to specific aims**

Analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC), IBM SPSS version 25 (SPSS, Chicago, IL) and R version 3.4.4 (R Development Core Team). When appropriate, the sampling approach will be accounted for through weighting.

**A.** Frailty categories assessed at baseline (T0; frail vs. robust) will serve as the exposure variable. Baseline characteristics across frailty index categories will be compared by chi-squared test for categorical variables and student-t-test for continuous variables. Cox proportional hazards regression models [62] will be fitted to evaluate the hazard ratios for death. Several adjustment methods will be applied including traditional multivariable adjustment and propensity score adjustment [63]. The incremental discriminatory ability of frailty index over demographic and SES variables in predicting death during a 12-year follow up will be evaluated by the c-statistic. Assessing the c-statistic and its corresponding standard error from Cox proportional hazards models will be performed with methods proposed by Harrell et al. [64].

**B.** Baseline characteristics across HEI categories as measured at T0 will be compared by chi-squared test for categorical variables and analysis of variance for continuous variables. The predictive role of nutritional indices in the long-term incidence of frailty, as assessed by two methods, cognitive decline and other outcomes will be assessed using logistic regression models [65]. Adjustment will be made for sociodemographic, clinical, and psychosocial variables, via either multivariable adjustment or propensity score [66]. Of the 1,799 participants in the initial survey, many are no longer able to participate in the T1 interview (death, loss to follow-up, non-response). Because frailty status could not be assessed among the latter group, selection bias is introduced [67]. This bias will be addressed through an adaptation of a marginal structural model, applying inverse probability weights [67 68]. Accordingly, the probability of original participants to take part in the second interview will be estimated. Each observation will then be weighted by the reciprocal (i.e., the inverse) of the predicted probability of participating at T1.

**C.** Nutrient intake will be calculated using the "Tzameret" program, as described previously. Data of nutrient consumption among current study participants will be compared with International recommendation, i.e., Dietary Reference Intake (DRI) [69 70]. Prevalence of malnutrition risk at T1 will be assessed by MNA-SF [53]. Changes in nutrient consumption will be evaluted by descriptive statistics and paired t-test will be used to evaluate the mean difference between HEI scores at T0 and T1.

**Approach to missing data**

The distribution of missing values will be examined. Depending on the extent of the problem, several approaches will be considered. In case of a low rate of missing data, a complete case analysis will be considered, i.e., removal of subjects where any of the predictor variables are missing. Otherwise, we will employ multiple imputation methodology [71]. For this purpose, the number of complete (imputed) datasets will be defined by the following formula: $(1+\lambda/m)^{-1}$= *efficiency*, where λ is the fraction of missing information and *m* the number of datasets to impute. We will assume an efficiency of 0.975. Missing values will be replaced by imputed values based on models incorporating demographic, socioeconomic, psychosocial, and clinical variables. The results of these datasets will then be combined using Rubin's rules [71].

**Estimated statistical power**

Among 1,800 initial participants, some 1,115 survived so far. About 600 subjects are expected to be re-interviewed, assuming a response rate of 55% for T1 interview. Considering frailty prevalence of over 35% at the estimated average age of 84 years in T1 interview[72], about 250 frail subjects can be expected. This sample size is sufficient for detecting an adjusted odds ratio for frailty of ≤ 0.60 between the upper and lower HEI score tertiles (significance level at 5% and power of 80%). Association of this magnitude was previously reported. For example, a previous 6-year follow-up study showed that adherence to MD diet was associated with lower odds of developing frailty [OR = 0.30 (95% CI: 0.14, 0.66)] [38].

**Patient and Public Involvement**

Patients and or public are not involved.

### Ethical aspect

Ethical approval for the study was obtained from the Helsinki Committee of Chaim Sheba Medical Center at Tel Hashomer and the Ethical Committee of Tel-Aviv University. Potential participants receive a preliminary letter with a description of the study, a request to participate and an announcement that telephone contact would be made in the near future. In addition, the letter provides the telephone number of the research coordinator for further questions. After a minimum of two weeks, potential participants are contacted by telephone in order to set an interview appointment for those who agree to participate. The interview does not involve clinical procedures, and no human biological specimens are collected. Therefore, participants' burden is minimal. Each interviewee is asked to sign an informed consent form.

### Dissemination

The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

## Discussion

The ILSA sets out to transform a large national survey of older adults with a broad-spectrum data into a cohort study with a specific age-related questionnaire including comprehensive geriatric assessment, evaluation of general health and quality of life. Obtaining data at two points in time, more than a decade apart, will allow us to evaluate long-term changes in older adults population and examine dietary role in the context of healthy aging and adverse clinical outcomes. Participants' estimated current mean age of 84 years old, defined as the "oldest-old", have over past decades been the most rapidly expanding segment of the population in developed countries and also the most susceptible to disease and disability [73]. Only few studies have explicitly examined the concept of robust aging among the oldest-old and investigated its heterogeneity in functioning, cognitive abilities, diet quality, and nutritional status changes. Both frailty and cognitive decline are at the core definition of healthy aging [19 20 74-76] and are highly prevalent in older people; still, as their status varies considerably among older adults, important issues such as how they develop, are they preventable, and can they be detected reliably have yet to be defined. Obviously, our study has several limitations. Of the 1,799 participants in the original survey, many are no longer able to participate in T1 interview (death, loss to follow-up, non-response). Because frailty status and cognitive state could not be assessed among the latter group, selection bias is introduced. This bias will be addressed through applying inverse probability weights based on estimated propensity score. Another limitation is the fact that dietary quality assessment (exposure variable) is based on a single

24-hour dietary recall. Although evaluation of the HEI score is suitable for a single 24-hour dietary recall intake [77 78], individual diets can vary greatly from day to day. Furthermore, we cannot preclude that participants may have changed their dietary habits during the follow-up. The 24-hour dietary recall tool is widely used to assess dietary intake in population studies since 1965 [79], with studies indicating its accuracy for estimating energy intake [51 80]. In addition, the multiple-pass 24-hour dietary recall technique, which is used in our study, mange to limit the extent of underreporting that occurs with single self-reported food intake [51 81]. Like most similar studies, self-report information and information form a proxy can lead to misclassification bias that may lead to under or overestimation of dietary recall, frailty and other measures. Nevertheless, examining the role of diet quality in the context of healthy aging and adverse clinical outcomes may help to broaden our knowledge regarding the older adults population, provide a scientific basis on which policymakers can rely and pave the way for early therapeutic interventions.

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**Figure legends:**

Figure 1: Study design sketch. [1]Mini Mental State Examination; [2]General Health Questionnaire; [3]Activities of Daily Living; [4]Mini Nutritional Assessment-Short Form; [5]Healthy Eating Index; [6]Geriatric Depression Scale; [7]Short Form of health-related-quality of life.

Figure 2: Sample size flow chart.

## Footnotes

### Authors' contributions

AG, study coordinator of the ILSA, drafted the manuscript, assisted in the conception of the study and led field activities and study monitoring; UG, co-investigator for the ILSA, conceived of the study concept and design and supervised the study; T Shohat, co-investigator of the ILSA and physician-in-charge of the study; LKB, principal investigator of MABAT ZAHAV survey; T Shimony, coordinator of MABAT ZAHAV survey; YG, principal investigator of the ILSA, conceived of the study concept and design and co-drafted the manuscript. All authors revised, reviewed and approved the final paper.

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**Competing interests**

The authors declare that they have no competing interests.

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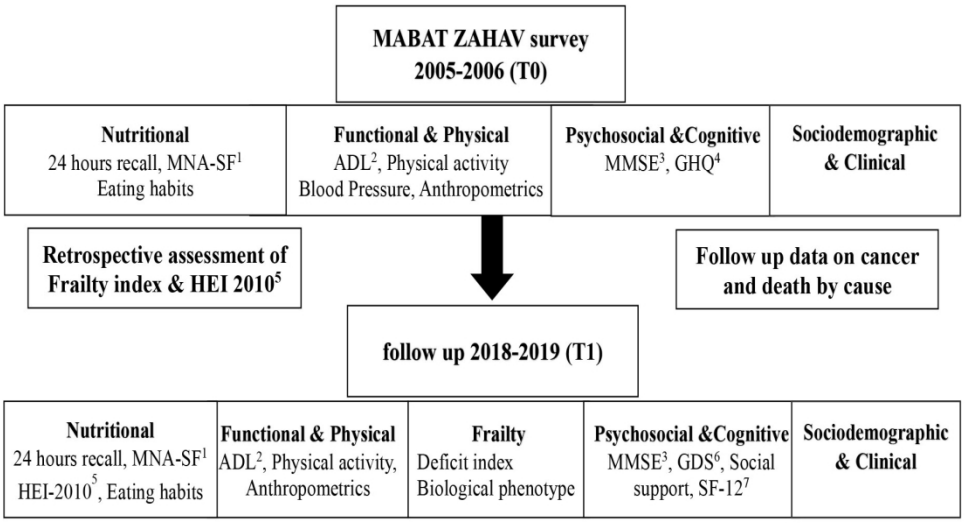


Figure 1: Research design sketch.[1]Mini Mental State Examination; [2]General Health Questionnaire; [3]Activities of Daily Living; [4]Mini Nutritional Assessment– Short Form; [5]Healthy Eating Index; [6]Geriatric Depression Scale; [7]Short Form of health-related-quality of life.

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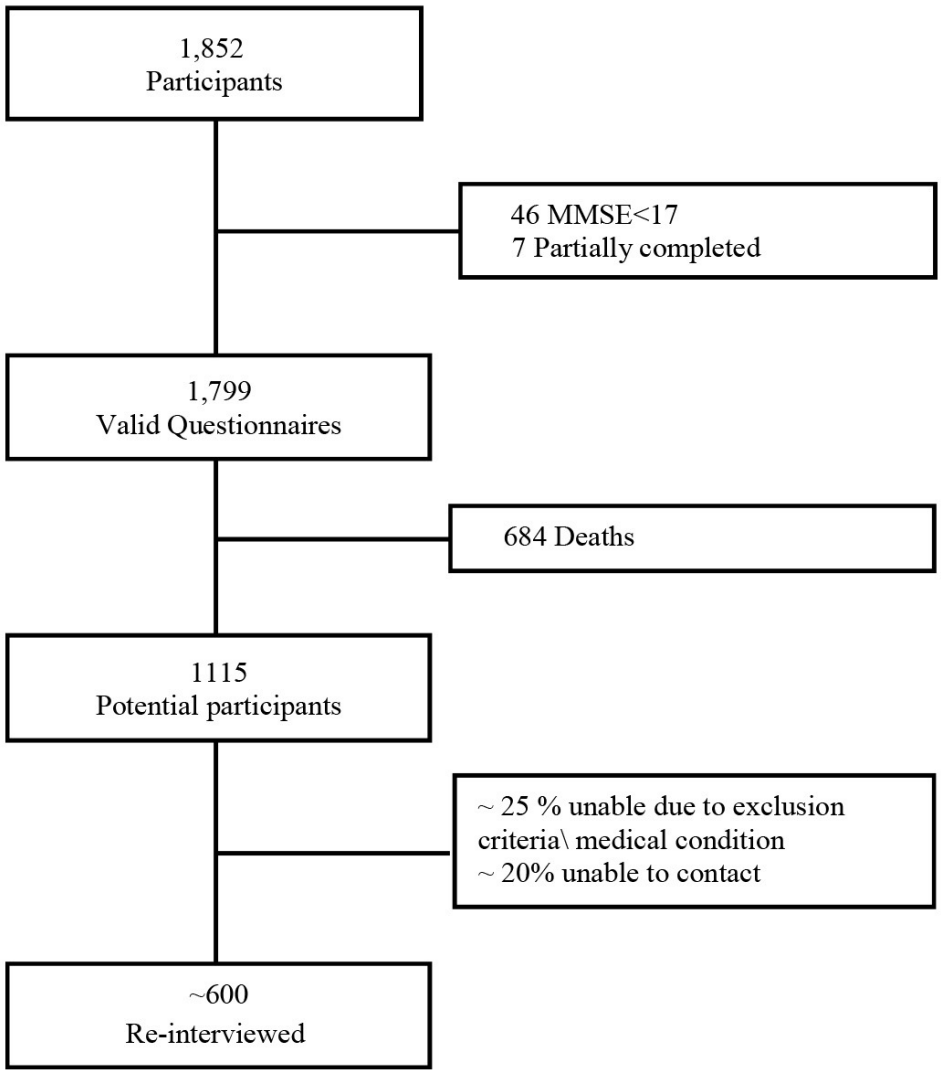


Figure 2. Sample size flow chart.

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# Diet Quality in Relation to Healthy Aging. The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

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# Diet Quality in Relation to Healthy Aging.

## The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

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# Diet Quality in Relation to Healthy Aging.

## The Israeli Longitudinal Study on Aging (ILSA): Study Protocol.

Introduction: Population aging is accelerating rapidly in Israel as well as worldwide, necessitating adaptation of the health care system and consideration of new approaches that serve the specific needs of older adults. In addition to cognitive function, frailty is one of the most challenging expressions of physical and mental aging, a multidimensional syndrome of increased vulnerability. Several studies have shown that low intake of certain micronutrients and protein is associated with higher risk of frailty and cognitive impairment. However, whether global diet quality is involved in the etiology of the latter outcomes is unclear.

Methods and analysis: We are conducting, among older adult subjects who took part in "MABAT ZAHAV" (Israeli National Health and Nutrition Survey of Older Adults) in 2005-2006 (T0, N=1,852) an extensive follow-up interview (T1) that includes comprehensive geriatric assessment and evaluation of general health and quality of life. Diet quality is evaluated using the Healthy Eating Index (HEI) 2010, based on 24-hour diet recall measured at T0 and T1. Frailty is assessed using two different approaches: the phenotype framework and the accumulation of deficits model. Cognitive function is assessed by Mini Mental State Examination (MMSE) and cognitive decline by the difference between repeated MMSE measurements. Different analytic methods will be applied to evaluate the role of diet quality in development of frailty and cognitive decline with inverse probability weighting used to minimize attrition bias. About 600 subjects are expected to be interviewed between May 2017 and December 2019.

Ethics and dissemination: Ethical approval was obtained from the Helsinki Committee of Sheba Medical Center, Tel Hashomer, Israel and the Ethical Committee of Tel-Aviv University. All participants sign an informed consent form. The findings of the study will be published in peer-reviewed journals.

Keywords: diet quality; epidemiology; older adults; healthy aging; longitudinal studies

## Strengths and limitations of this study

- The study transforms a large national survey of older adults with a broad-spectrum data into a cohort study with a specific age-related questionnaire including comprehensive geriatric assessment.
- Obtaining data at two points in time, more than a decade apart, will allow us to evaluate long-term changes in older adult population and examine adverse clinical outcomes.
- Selection bias due to death, loss to follow-up and non-response.
- Misclassification bias due to self-report data and nutritional assessment which is based on a single 24-hour dietary recall.

## Background

### Healthy aging

Population aging is accelerating rapidly in Israel as well as worldwide, necessitating adaptation of the health care systems and consideration of new approaches that serve the specific needs of older adults [1]. According to current forecasts, the percentage of persons 65 years and older will increase from 8.5% in 2015 to 19.0% by 2030 [2]. The concept of healthy aging is generally described as optimizing opportunities for improving and preserving health and physical, social, and mental health; and enhancing successful life-course transitions [3]. While this definition depicts healthy aging (also termed successful aging) as a complex process of adaptation to changes across the lifespan, the concept needs to be looked at in terms of a measurable outcome that can be empirically validated [4]. Despite the differences in healthy aging definitions, there is some consensus in the studies that 'successful ager' outcome should measure function in domains of cognitive, physical and mental well-being [4]. In our study, we intend to transform a large national survey of older adults into a cohort study with specific age-related questionnaires including general health, functional status, quality of life, social support, depression and cognitive function. Healthy aging will be assessed by various measurements, with emphasis on frailty state and cognitive function. The predictive role of diet quality in the devlopment of the latter outcomes will be evaluted, as described in detail in the following sections.

## Frailty

Frailty is recognized as an important medical syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems [5]. Frail older persons are at high risk of accelerated physical and cognitive functional decline, disability, and death [6]. The concept of frailty adopts an integrative approach which represents general properties of aging and health rather than particular functional deficiency or decline [7].

Assessment of frailty has implications both for the individual and on society at large, forecasting healthcare use [8 9] and providing opportunities for preventive intervention [10 11], thus making it a key issue in chronic disease management and healthy aging [12 13].

Methods to measure frailty vary throughout the literature [14-17], with two principal models of frailty emerging: **(1)** The Fried and colleagues' *Biological Phenotype* [5] framework, which conceptualizes frailty as a biologic syndrome characterized by a decline in overall function and loss of resistance to stressors. This model is comprised of five physical indicators including low physical activity, weak grip strength, slow walking speed, exhaustion, and unintentional weight loss**. (2)** The Rockwood and colleagues' *Accumulation of Deficits* Index [18], which defines frailty as the cumulative effect of individual deficits. Under this model, frailty is measured by ~40 parameters of disease states, functional status, cognitive function, and psychosocial status, collectively referred to as deficits. The index is a calculation of the presence or absence of each deficit as a proportion of total [8]. Frailty and successful aging models share common aspects of aging [19]. Frailty is recognized as an independent determinant of successful aging, supporting the idea that successful agers might be nonfrail individuals [19 20].

## Cognitive function

Another important aspect of successful aging is the maintenance of cognitive function [21]. Cognitive function is a predictor of independence and quality of life [22]. Cognitive function assessed repeatedly is important because it is possible for an elderly person to have a normal cognitive score that still represents a significant decline for that individual. Mild cognitive impairment (MCI) is a syndrome that is currently thought of as a transition phase between healthy cognitive aging and dementia [23]. MCI is defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with Activities of Daily Life (ADL) [24]. The estimated prevalence of MCI in population-based studies ranges from 10% to 20% in people older than 65 years of age. Clinical studies indicate that older adults with MCI will progress to Alzheimer's Disease (AD) at a rate of 10% to 15% per year, compared with healthy control subjects who convert at a rate of 1% to 2% per year [25], making it an area of intense interest for theoretical and practical reasons. A widely

recognized instrument for detection of cognitive impairment is the Mini-Mental State Examination (MMSE) [26 27]. The MMSE consists of thirty questions and has a maximum score of 30 points. MCI will be assessed according to poor performance on MMSE (i.e., a score of 1.5 standard deviations below the age- and education-specific mean) and presereved independence in functional abilities [27 28].

**Nutrition**

Nutrition is an important element that affects and is affected by the aging process [29 30]. Malnutrition is highly prevalent among older adults and associated with a general decline in physical and mental functioning, higher hospitalization rate and increased mortality [29]. Eating patterns of various cultures around the world have been associated with risk for chronic diseases [31]. However, examining the intake of a single nutrient or food group does not account for the complexity of dietary intake, as food and nutrients are not eaten in isolation. Consequently, indices of dietary quality, patterns, and variety are increasingly used by nutritional epidemiologists [32]. The Healthy Eating Index-2010 (HEI-2010) [33] is such an index, originally released in 1995 and then updated in 2010 by the US Department of Agriculture (USDA) as a measure of diet quality. The concept of diet quality as a determinant of frailty development is not new but whether it is a predictor or consequence of frailty has not been investigated adequately [34]. Several studies have shown that low intake of certain micronutrients and protein is associated with a higher risk of developing frailty. However, very few studies have assessed the effect of overall diet quality on frailty [35]. Two studies have suggested that increasing adherence to Mediterranean diet (MD, a diet characterized by high intake of fish, vegetables, legumes, fruits, cereals, and unsaturated fatty acids [36]) is associated with decreasing risk of frailty among community-dwelling older adults in Spain and Italy [37 38]. In addition, it was recently demonstrated that higher adherence to MD is associated with lower AD risk [39 40]. However, in most studies the MD score was defined from sample-specific scores; thus, only the relative but not the absolute effect of MD was assessed, and the results of these studies are difficult to compare across populations.

## Research Objective

### General objective

Investigate the relationship between diet quality and healthy aging.

### Specific aims

**A.** Develop a frailty index based on "Mabat Zahav" data (T0) and evaluate its prevalence and association with subsequent survival.

**B**. Examine the predictive role of diet quality in development of frailty, cognitive changes and other healthy aging aspects among study participants.

**C.** Investigate long-term changes of dietary consumption and nutritional status among study participants.

### Hypothesis

We hypothesize that diet quality in older adults is predictive of successful aging as measured by a variety of clinical outcomes.

## Methods/Design

### Research design

The study employs a cohort study design. It constitutes the second interview of Mabat Zahav study [41]. The First National Health and Nutrition Survey of Older Adults Aged 65 and Over in Israel ("Mabat Zahav") was carried out in 2005-2006 by the Israel Center for Disease Control (ICDC) and the Nutrition Department of the Israel Ministry of Health. The data collected on the survey included information regarding health and nutrition status, health behaviors (physical activity, alcohol consumption, medication use, use of nutrition supplements), knowledge and attitudes regarding nutrition, and utilization of health services. The survey framework and population is further described in the following section. The current study questionnaire (T1) duplicates most parts of the original (T0) interview (Fig. 1). In addition, measurements pertaining to frailty status and cognitive function are performed, as well as psychosocial assessments including the multidimensional scale of perceived social support (MSPSS) [42], geriatric depression scale (GDS) [43] and the short form of health-related-quality of life (SF-12) [44].The added psychosocial questionnaires are in order to enable a more comprehensive analysis of the concept of healthy aging and well-being. The HEI-2010, a measure of diet quality retrospectively assessed at T0, will serve as the exposure variable and be assessed prospectively at T1 in order to evaluate general changes in diet quality and composition.

Frailty at T0 is retrospectively assessed through the Rockwood and colleagues' Deficit Index [18]. The index will be developed according to published criteria in order to identify frail participants at study entry. Frailty will be assessed prospectively at T1 by both the Deficit Index and the Fried and colleagues' Biological Phenotype framework [5]. Cognitive changes and MCI will be assessed prospectively. Mortality follow up will be conducted among T0 participants through linkage to the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers.

**"Mabat Zahav" survey – study population**

The Mabat Zahav survey population was a random sample of Israeli citizens age ≥ 65 years old. The survey included 1,852 community-dwelling participants (1,536 Jews and 316 Arabs) residing in Israel, who had lived in the country for at least one year in urban and rural settlements with more than 20,000 residents. Exclusion criteria of Mabat Zahav survey included: significant cognitive reduction (MMSE<17) and hospitalization at the time of the study. Survey methods included a personal interview in the interviewees' homes or sheltered accommodation using a structured questionnaire.

Sampling frame: Adults aged 65 and over insured by the two major HMO in Israel, Clalit Health Services and Maccabi Health Services, representing 86.3% of all of the elderly in Israel, were sampled. Oversampling was carried out in the Arab population, because of the small percentage of elderly in the Arab population (6.3%), in order to ensure a sample large enough for statistical analyses and comparisons with the Jewish sector. The overall sample size target was 1,800 participants, 1,500 Jews, and 300 Arabs.

Sampling method: Lists of insured older adults from each of the two HMO were combined and divided into population groups (Jews and Arabs). Sampling was carried out in two stages due to low response rate at the first stage, in order to meet the sample size target. First stage: 5,100 people were randomly sampled, with 4,250 from the Jewish list and 850 from the Arab list. Interviewing of individuals from the first sample commenced in July 2005. A total of 1,081 individuals were interviewed, of which 1,051 questionnaires met inclusion criteria (909 Jews and 142 Arabs). Second stage: An additional sample was drawn in January 2006, including 4,250 Jews and 2,500 Arabs, since the initial lists were exhausted. A total of 771 individuals were interviewed, of which 748 questionnaires met inclusion criteria (590 Jews and 158 Arabs). The interviews were held in multiple languages, and the questionnaires were translated accordingly: 1277 (69%) in Hebrew, 316 (17%) in Arabic, 257 (14%) in Russian and 2 in English [41]. All data collected are available online at the ministry of health government web site [45].

**Exclusion criterion in current research stage (T1):**

Significant cognitive reduction as measured by a MMSE score of less than 17 [26 46] or inability to communicate.

**Sample size**

Among T0 initial participants (1,852), 1,799 (1,499 Jews and 300 Arabs) questionnaires were included in the final survey analysis. Forty-six participants (29 Jews and 17 Arabs) had a MMSE score of less than 17 (after adjustment for age and education), and seven questionnaires were only partially completed and therefore excluded from the statistical analysis. According to the mortality registry of the Ministry of Health, 1,115 participants were alive in February 2017. We assume that 25% of candidates will be unable to participate due to either exclusion criteria or severe medical condition and another 20% could not be contacted due to address or telephone number changes. We expect a response rate of 55%-60% among the remaining candidates for T1 interview, and so about 600 subjects are expected to be re-interviewed (Fig.2). Our efforts to maximize recruitment include the following steps:

Disconnected phone numbers and no response: **a.** Locating address changes via the Ministry of Interior database. **b.** Searching by the Israeli non-commercial telephone directory according to city of residence and family name only (in case of incorrect street name). **c.** Conducting ten attempts to contact each non-respondent.

Refusal: We are trying to encourage cooperation by **a.** Offering to conduct interviews 7 days a week, morning times and afternoons. **b.** Offering to divide the interview into two separate times, in case the length of the interview is a concern for the participant.

**Data collection**

A personal interview is conducted in the interviewees' homes by trained interviewers using a structured questionnaire. Anthropometric measurements are performed using standardized protocols as described in a subsequent section. Interviews are conducted in Hebrew, Arabic or Russian. Estimated time of an interview is an hour and a half. In case the participant is unable to complete the questionnaire by himself/herself, but still meets inclusion criteria, information from a proxy is obtained regarding dietary intake, chronic diseases, ADL, sociodemographic status and medication use. The proxy interview does not include the following assessments: GDS, SF-12, MSPSS and self-rated health. All data (except the 24-hour dietary recall) are collected using KoBotoolbox [47] software which is a freely available application to design surveys for data collection through smart devices

and run on Android based platforms. The data are exported into a password protected Excel file on a daily basis. All responses are typed directly during the interview through Lenovo TAB2 A10-30 tablet. The 24-hour dietary recall is handwritten before being typed to "Tzamert" program [48], an Israeli nutrient data program, which enables recording of food intake and calculation of nutrient intake. In case of any technical difficulties, the questionnaire is completed manually by the interviewer. A pilot study (n=30) was conducted, after which questionnaires undertook minor adjustments.

Exposure variable: The HEI-2010 score at baseline (T0): Dietary data from the 24-hour dietary recall questionnaire was entered into the "Tzamert" program. The program uses the nutrient data in the BINAT program- the Israeli nutrient database which is maintained and updated by the Nutrition Department of the Ministry of Health. An HEI-2010 score [32] will be calculated for T0 and T1 interviews separately. The HEI-2010 has twelve components, nine of which assess adequacy of the diet, including 1) total fruit; 2) whole fruit; 3) total vegetables; 4) greens and beans; 5) whole grains; 6) dairy; 7) total protein foods; 8) seafood and plant proteins; and 9) fatty acids. The remaining three: refined grains, sodium, and empty calories assess dietary components that should be consumed in moderation. For each component, the respondents receive a minimum score of 0 and a maximum score of 5 or 10 (for perfect adherence to recommendations); intermediate degrees of adherence are calculated proportionately. Thus, the overall index has a range from 0 (worst) to 100 [32].

Nutritional status assessments:

(1) Dietary recall: The multiple-pass 24-hour dietary recall questionnaire is administrated**.** The method was originally developed by the USDA in order to limit the extent of underreporting that occurs with self-reported food intake [49]. The interviewer uses three distinct passes to gather information about a subject's food intake during the preceding 24 hours. The first pass is termed the *quick list*; here the interviewees are asked to recall all they had eaten and drunk in the 24-hour period that preceded the interview. The second pass is termed the *detailed description*. In this pass, the interviewees are asked to clarify any foods mentioned in the quick list. The third pass is termed the *review*. The interviewer reviews the list of foods mentioned and probes for additional eating occasions and clarifies food portion sizes [49]. In order to assist the interviewees in identifying food types and quantities during the interview, the interviewers use the "Food and Food Quantities Guide" which is partially based on the Food Guide of the USDA. The guide includes detailed questions on foods, as well as many photographs of Israeli foods. In order to

facilitate quantification of amounts consumed, the interviewers use, in addition to the guide, identification aids such as a measuring cup, tablespoon, and teaspoon.

(2) Food security: Household food security is defined as a situation whereby all household members have access at all times to a food supply which is adequate for a healthy active life. Food security is assessed using the short 6-item food security USDA questionnaire [50].

(3) Malnutrition risk: Modified Mini Nutritional Assessment-Short Form (MNA-SF) [51]. The 6-item questionnaire is a nutritional screening tool that assesses malnutrition risk.

Primary outcomes:

Frailty assessment: Frailty at T0 and T1 is assessed by the *Deficit Index* model [18]. Under this model, frailty is measured by ~40 parameters of symptoms, signs, disease states and disabilities, collectively referred to as deficits. Adapting the Rockwood index of accumulation of deficits method [7] with T0 data, a Frailty Index (FI) was developed comprising 33 variables. The FI at T1 will comprise the same variables as T0 FI and will serve as the outcome measure. The FI is a calculation of the presence or absence of each deficit as a proportion of the total. Dichotomous items are coded as 0 if the deficit is absent and as 1 if it is present, while ordinal variables are graded into a score between 0 and 1 (0 representing no impairment, 0.5 for minor impairment, and 1 for major impairment). Scores are then summed up and divided by the total number of variables, yielding a frailty index between 0 and 1, with 1 representing the greatest frailty (a threshold of ≥0.25 is typically used to define frailty) [52]. Frailty at T1 is additionally assessed by the *Biological Phenotype* model [5]. Frailty using this instrument is identified by the presence of three or more of the following components: 1. Shrinking: weight loss, unintentional, of more than 4.5 Kg, or more than 5% of body weight, in the previous year; 2. Weakness: grip strength in the lowest 20% (adjusted for sex and body mass index); 3. Poor endurance and energy: as indicated by self-report of exhaustion; 4. Slowness: the slowest 20% of the participants in the sample, based on time of a 5-meter walk (adjusted for sex and standing height); 5. Low physical activity level: a weighted score of kilocalories expended per week will be calculated based on a Physical Activity Scale for the Elderly (PASE) questionnaire [53]. The lowest quintile of physical activity will be identified for each gender.

Cognitive assessment**:** Cognitive status is evaluated using the MMSE [26]. The questions are grouped into seven categories, each representing a different cognitive domain or function: orientation to time (5 points); orientation to place (5 points); registration of three words (3 points); attention and calculation (5 points); recall of three words (3 points); language (8 points) and visual construction (1 point) [54]. The MMSE scores (maximum, 30 points) will be education- and age-standardized [46]. Some

participants cannot complete test items due to physical disability. The MMSE in these subjects will be scored out of the items that can be tested [55]. Cognitive impairment will be defined as a score < 24 [26]. Cognitive decline will be calculated as the MMSE score difference between 2005 and 2017 and will be defined by the 10% of the sample who declined the most (i.e., the 90$^{th}$ percentile of decline). MCI will be assessed according to poor performance on MMSE and preserved functional independence [28]. Poor performance on MMSE will be defined by a score of 1.5 standard deviations below the age- and education-specific mean. Preserved functional independence will be defined according to Katz et al. scale of ADL score [27 28].

Secondary outcomes:

Health status evaluation: The questionnaire includes data on self-rated health (current status and recent changes) and chronic diseases (e.g., cardiovascular diseases, Parkinson's disease, respiratory diseases, renal disease, cancer, glaucoma and cataract, diabetes mellitus, osteoporosis, hypertension). In addition, the questionnaire includes demographic details, alcohol consumption, and smoking habits information.

Assessment of disabilities: Function is assessed by the Katz scale of Activities of Daily Living [56] based on ability to dress, shower/bathe, sit down and rise from a chair, eat and go to the bathroom. The maximum score is 15, with a score of 5 indicating "no functional limitations," a score of 6-10 indicating some functional limitations, and a score of 11 or more indicating several functional limitations.

Psychosocial assessments: Assessments include depression, perceived social support and health-related quality of life. Depression is evaluated via a 5-item short form of the Yesavage GDS [43]. A score of 2 or higher indicates possible depression. Social support is assessed through the MSPSS [57], a 12-item questionnaire designed to measure perceptions of support from three sources: family, friends and a significant other (4 items for each source). Answers are given on a 1-7 scale. Weighted scores are calculated by averaging the specific items, each scale (source) individually and the entire questionnaire. A high score represents a high level of perceived social support. Health-related quality of life is evaluated via SF-12 [44], physical (PCS) and mental (MCS) component scores will be constructed from SF-12, using standard (U.S.) and country-specific scoring algorithms.

Drugs: The participants are asked about any medication use on a regular basis (prescription as well as over-the-counter drugs). In the preliminary letter, the participants are asked to prepare their

regular medication list. Medications are coded using the ATC (Anatomical Therapeutical and Chemical) system, developed by the World Health Organization (WHO) [41].

Anthropometric measurements: Include standing height and weight, ulna length (to calculate height, using recognized formulae [58]), waist and mid-upper arm circumference. Weight measurements are carried out using an analog scale suitable for weighing up to 130 kg, with accuracy to 0.5 kg. The scales are placed on an uncarpeted floor and calibrated before weighing. Height is measured using a spring coil measuring tape. Waist circumference is measured using a flexible tape, with the ability to measure up to 150 cm, at the narrowest part of the torso, where a "fold" is created when bending sideways [41]. Mid-upper arm circumference is measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromion) using a flexible tape [59].

Blood pressure and pulse measurements: The interviewers conduct blood pressure and pulse measurements using an electronic monitor. The measurements are carried out according to a protocol based on recommendations of the American Heart Association [60]. Sitting blood pressure and pulse are measured in the right arm and is carried out twice, with a minute rest in-between. In case of a difference of 10% or more between measurements of either systolic or diastolic pressure, a third measurement is carried out. The final value will be the mean of measurements.

Mortality and cause of death: Original participants were linked to the nationwide database of causes of death (compiled by the Central Bureau of Statistics) via their national identification numbers. Mortality information is managed by the Ministry of Health. Since 1999, deaths are coded according to the International Classification of Diseases, Tenth Edition (ICD-10).

**Quality assurance**

Quality assurance is carried out in various ways: (1) A pilot study (n=30) was conducted, after which questionnaires and research tools were finalized; (2) Interviewer training: A 2-day seminar were designed and included standard procedures of administrating research questionnaires, performing anthropometric measurements and handling data in general; (3) All interviews (under interviewee consent) are recorded; (4) The study coordinator randomly monitor 5-10% of all interviews; (5) Dietary data quality assurance includes: ***a.*** a food recall check: time sequence, completeness of information, matching of the items in the "Quick List" with those in the "Comprehensive List", and ***b***. following data entry into the Tzamert program, testing will be performed for outliers, in

appropriate quantities, lack of correlation between meal times and types, and missing quantities and incorrect coding.

**Statistical analysis according to specific aims**

Analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC), IBM SPSS version 25 (SPSS, Chicago, IL) and R version 3.4.4 (R Development Core Team). When appropriate, the sampling approach will be accounted for through weighting.

**A.** Frailty categories assessed at baseline (T0; frail vs. robust) will serve as the exposure variable. Baseline characteristics across frailty index categories will be compared by chi-squared test for categorical variables and student-t-test for continuous variables. Cox proportional hazards regression models [61] will be fitted to evaluate the hazard ratios for death. Several adjustment methods will be applied including traditional multivariable adjustment and propensity score adjustment [62]. The incremental discriminatory ability of frailty index over demographic and SES variables in predicting death during a 12-year follow up will be evaluated by the c-statistic. Assessing the c-statistic and its corresponding standard error from Cox proportional hazards models will be performed with methods proposed by Harrell et al. [63].

**B.** Baseline characteristics across HEI categories as measured at T0 will be compared by chi-squared test for categorical variables and analysis of variance for continuous variables. The predictive role of nutritional indices in the long-term incidence of frailty, as assessed by two methods, cognitive decline and other outcomes will be assessed using logistic regression models [64]. Adjustment will be made for sociodemographic, clinical, and psychosocial variables, via either multivariable adjustment or propensity score [65]. Of the 1,799 participants in the initial survey, many are no longer able to participate in the T1 interview (death, loss to follow-up, non-response). Because frailty status could not be assessed among the latter group, selection bias is introduced [66]. This bias will be addressed through an adaptation of a marginal structural model, applying inverse probability weights [66 67]. Accordingly, the probability of original participants to take part in the second interview will be estimated. Each observation will then be weighted by the reciprocal (i.e., the inverse) of the predicted probability of participating at T1.

**C.** Nutrient intake will be calculated using the "Tzameret" program, as described previously. Data of nutrient consumption among current study participants will be compared with International recommendation, i.e., Dietary Reference Intake (DRI) [68 69]. Prevalence of malnutrition risk at T1 will be assessed by MNA-SF [51]. Changes in nutrient consumption will be evaluted by descriptive statistics and paired t-test will be used to evaluate the mean difference between HEI scores at T0 and T1.

**Approach to missing data**

The distribution of missing values will be examined. Depending on the extent of the problem, several approaches will be considered. In case of a low rate of missing data, a complete case analysis will be considered, i.e., removal of subjects where any of the predictor variables are missing. Otherwise, we will employ multiple imputation methodology [70]. For this purpose, the number of complete (imputed) datasets will be defined by the following formula: $(1+\lambda/m)^{-1}$= *efficiency*, where λ is the fraction of missing information and *m* the number of datasets to impute. We will assume an efficiency of 0.975. Missing values will be replaced by imputed values based on models incorporating demographic, socioeconomic, psychosocial, and clinical variables. The results of these datasets will then be combined using Rubin's rules [70].

**Estimated statistical power**

Among 1,800 initial participants, some 1,115 survived so far. About 600 subjects are expected to be re-interviewed, assuming a response rate of 55% for T1 interview. Considering frailty prevalence of over 35% at the estimated average age of 84 years in T1 interview[71], about 250 frail subjects can be expected. This sample size is sufficient for detecting an adjusted odds ratio for frailty of ≤ 0.60 between the upper and lower HEI score tertiles (significance level at 5% and power of 80%). Association of this magnitude was previously reported. For example, a previous 6-year follow-up study showed that adherence to MD diet was associated with lower odds of developing frailty [OR = 0.30 (95% CI: 0.14, 0.66)] [38].

**Patient and Public Involvement**

Patients and or public are not involved.

## Ethical aspect

Ethical approval for the study was obtained from the Helsinki Committee of Chaim Sheba Medical Center at Tel Hashomer and the Ethical Committee of Tel-Aviv University. Potential participants receive a preliminary letter with a description of the study, a request to participate and an announcement that telephone contact would be made in the near future. In addition, the letter provides the telephone number of the research coordinator for further questions. After a minimum of two weeks, potential participants are contacted by telephone in order to set an interview appointment for those who agree to participate. The interview does not involve clinical procedures, and no human biological specimens are collected. Therefore, participants' burden is minimal. Each interviewee is asked to sign an informed consent form.

## Dissemination

The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

# Discussion

The ILSA sets out to transform a large national survey of older adults with a broad-spectrum data into a cohort study with a specific age-related questionnaire including comprehensive geriatric assessment, evaluation of general health and quality of life. Obtaining data at two points in time, more than a decade apart, will allow us to evaluate long-term changes in older adults population and examine dietary role in the context of healthy aging and adverse clinical outcomes. Participants' estimated current mean age of 84 years old, defined as the "oldest-old", have over past decades been the most rapidly expanding segment of the population in developed countries and also the most susceptible to disease and disability [72]. Only few studies have explicitly examined the concept of robust aging among the oldest-old and investigated its heterogeneity in functioning, cognitive abilities, diet quality, and nutritional status changes. Both frailty and cognitive decline are at the core definition of healthy aging [19 20 73-75] and are highly prevalent in older people; still, as their status varies considerably among older adults, important issues such as how they develop, are they preventable, and can they be detected reliably have yet to be defined. Obviously, our study has several limitations. Of the 1,799 participants in the original survey, many are no longer able to participate in T1 interview (death, loss to follow-up, non-response). Because frailty status and cognitive state could not be assessed among the latter group, selection bias is introduced. This bias will be addressed through applying inverse probability weights based on estimated propensity score. Another limitation is the fact that dietary quality assessment (exposure variable) is based on a single

24-hour dietary recall. Although evaluation of the HEI score is suitable for a single 24-hour dietary recall intake [76 77], individual diets can vary greatly from day to day. Furthermore, we cannot preclude that participants may have changed their dietary habits during the follow-up. The 24-hour dietary recall tool is widely used to assess dietary intake in population studies since 1965 [78], with studies indicating its accuracy for estimating energy intake [49 79]. In addition, the multiple-pass 24-hour dietary recall technique, which is used in our study, mange to limit the extent of underreporting that occurs with single self-reported food intake [49 80]. Like most similar studies, self-report information and information form a proxy can lead to misclassification bias that may lead to under or overestimation of dietary recall, frailty and other measures. Nevertheless, examining the role of diet quality in the context of healthy aging and adverse clinical outcomes may help to broaden our knowledge regarding the older adults population, provide a scientific basis on which policymakers can rely and pave the way for early therapeutic interventions.

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**Figure legends:**

Figure 1: Study design sketch. [1]Mini Mental State Examination; [2]General Health Questionnaire; [3]Activities of Daily Living; [4]Mini Nutritional Assessment-Short Form; [5]Healthy Eating Index; [6]Geriatric Depression Scale; [7]Short Form of health-related-quality of life.

Figure 2: Sample size flow chart.

## Footnotes

### Authors' contributions

AG, study coordinator of the ILSA, drafted the manuscript, assisted in the conception of the study and led field activities and study monitoring; UG, co-investigator for the ILSA, conceived of the study concept and design and supervised the study; T Shohat, co-investigator of the ILSA and physician-in-charge of the study; LKB, principal investigator of MABAT ZAHAV survey; T Shimony, coordinator of MABAT ZAHAV survey; YG, principal investigator of the ILSA, conceived of the study concept and design and co-drafted the manuscript. All authors revised, reviewed and approved the final paper.

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### Competing interests

The authors declare that they have no competing interests.

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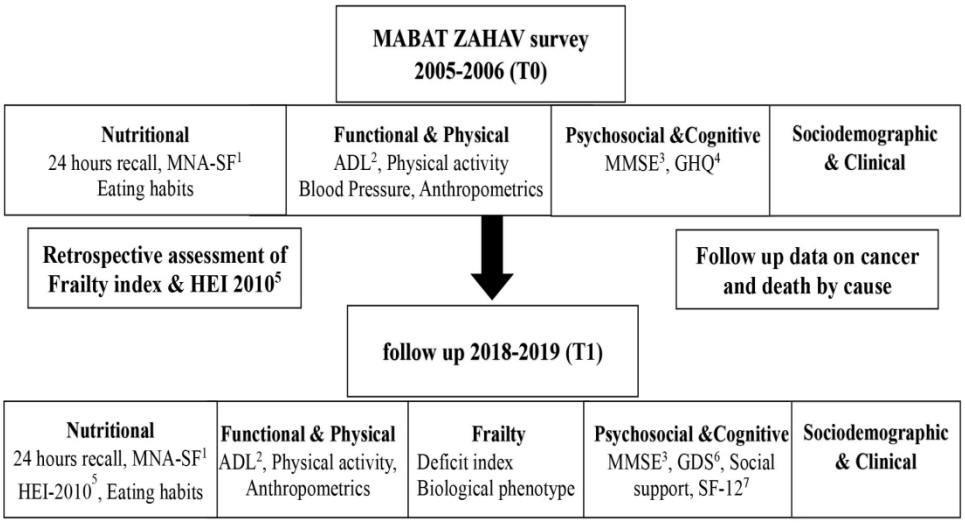


Figure 1: Research design sketch.[1]Mini Mental State Examination; [2]General Health Questionnaire; [3]Activities of Daily Living; [4]Mini Nutritional Assessment– Short Form; [5]Healthy Eating Index; [6]Geriatric Depression Scale; [7]Short Form of health-related-quality of life.

162x91mm (300 x 300 DPI)

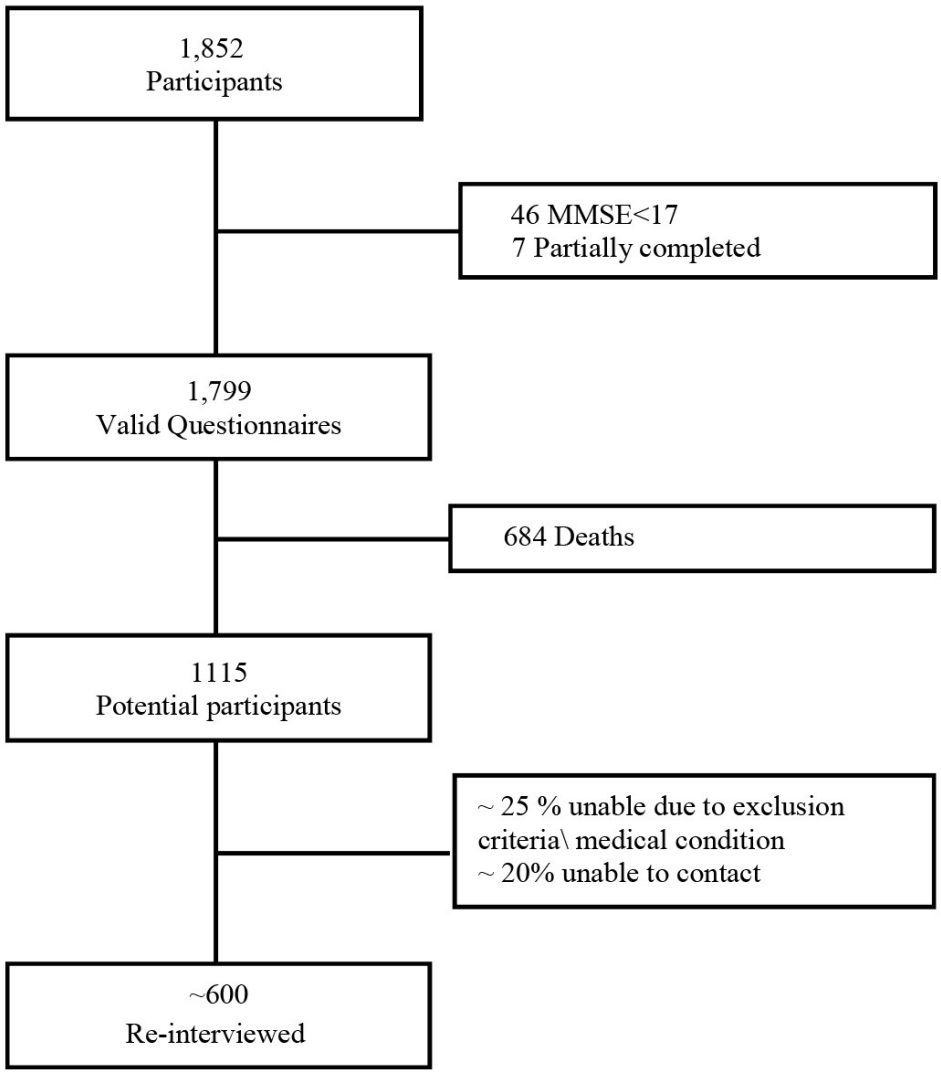


Figure 2. Sample size flow chart.

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