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INVESTIGATION INTO THE ENVIRONMENTAL RISK FACTORS OF ALZHEIMER'S DEMENTIA WITH EARLY ONSET AND OTHER NEURODEGENERATIVE DISEASES: AN ITALIAN CASE-CONTROL STUDY

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Abstract

Background and aim: Dementia is a progressive neurodegenerative disease generally affecting subjects in the elderly. However, it may occur also at younger age before 65 years, yielding a condition called early onset dementia (EOD). In recent years both prevalence and incidence of EOD has increased, including in Italy. Apart identification of few genetic factors, the etiology of dementia is largely unknown. This study aims at evaluating the role of environmental factors on the risk of Alzheimer's dementia with early onset and other neurodegenerative diseases in a Northern Italy population.

Methods: Using a case-control design, we identified newly-diagnosed EOD cases in the period 2016-2019 in Modena province, while the referent population was recruited from caregivers of subjects with dementia. We investigated potential risk factors related to environmental exposure, occupational activities, and dietary habits through two tailored questionnaires. The first one collected information about personal characteristics, clinical and family history of diseases and comorbidities, occupational history, hobbies and other leisure activities, residential history, and domestic use of pesticides. We also assessed EOD risk for exposure to light at night (LAN) using satellite data into a geographical information system. Finally, we assessed dietary habits by administrating a validated semi-quantitative food frequency questionnaire evaluating adherence to dietary patterns, namely the Greek-Mediterranean, the Dietary Approaches to Stop Hypertension (DASH), and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets.

Results: We eventually recruited 58 EOD cases (32 with Alzheimer's dementia and 19 with fronto-temporal dementia) and 54 controls. Most of the investigated exposures, such as occupational exposure to aluminum, pesticides, dyes, paints or thinners, were associated with increased odds ratio (OR) for FTD but not for AD. Long-term use of selenium-containing dietary supplements was associated with increased OR for EOD and, particularly, for FTD. For both EOD forms, smoking and playing football showed increased odds ratio, while cycling was associated with increased risk only in FTD. Overall sports practice appeared to be a protective factor for both dementia types.

About LAN exposure, we found an increase in risk at intermediate exposure categories, though further higher levels of LAN did not show similar OR increase.

Concerning dietary patterns, EOD risk linearly decreased with the increasing adherence to the MIND pattern. On the other hand, an inverse association for the Mediterranean and DASH diets emerged, but only at very high adherence levels.

Conclusions: Our study provides support for a positive association with EOD risk of previous head trauma, atrial fibrillation, stroke, diabetes and dyslipidemia. Regarding occupational factors, our findings suggest that use of pesticides, dyes/paints, and metalloids such as aluminum and selenium could be associated with increased disease risk, while no clear association emerged for environmental risk factors including LAN exposure, with the exception of a higher risk associated with smoking. Finally, adherence to the MIND dietary pattern may linearly decrease EOD risk. Despite some study limitations due to case-control design, including possible occurrence of selection and recall bias but likely to a limited extent, our findings highlighted a possible role of some environmental and lifestyle risk factors in the etiology of early onset dementia.

Keywords: Alzheimer's dementia; diet; environmental factors; light at night; early onset.

Introduction

Dementia is a chronic progressive syndrome characterized by the deterioration of cognitive function, i.e. the ability to process thoughts, beyond what it might be expected from the normal ageing. Dementia can affect memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is generally not affected. The impairment of cognitive functions is generally present along with the deterioration of emotional control, social behavior, or motivation. Dementia is one of the major disease leading to disability and dependency among older subjects in both high and low income countries. In addition, dementia is a burden not only for the affected subjects, but also for their families and especially for subjects' caregivers. The impact of dementia on both family and society can have several consequences on physical, psychological, social and economic areas [1]. For these reasons, dementia is a major public health issue which is growing worldwide due to the increasing ageing of several populations. However, the high incidence and prevalence of dementia in the elderly should not downgrade the relevance of its occurrence in younger subjects [2].

Early onset dementia

Dementia is generally considered a typical disease of the elderly. However, it can also affect young people. The term "presenile dementia", has been widely used in the literature until the early 90' but in recent years it is no longer appropriate and new terms have begun to be used, namely "early onset dementia", "young onset dementia", "younger onset dementia", and "younger people with dementia". The cutpoint for the young onset has been set at 65 years. Subjects with onset of dementia symptoms before this cutpoint are considered with early onset dementia (EOD), while for onset after 65 years they are considered as late onset dementia (LOD). This cutpoint has been chosen mainly for the social implication due to the age generally considered as the end of employment and beginning of the retirement. However, it is an arbitrary division and it has no specific biological relevance [2, 3].

The diagnosis of dementia has been mainly focused on symptoms characterizing older population. Indeed, the standard criteria for dementia diagnosis are based on the impairment of cognition as high to compromise the social and occupational functioning along with the impairment of memory [2]. EOD is a group of heterogeneous cognitive disorders characterized by different features compared to late onset dementia (LOD). As a consequence, diagnosis of EOD is generally more challenging, it is often misunderstood with other disorders especially at the early stages of the disease, leading to a delay in its diagnosis and an inadequate treatment [3].

Epidemiology

The prevalence of EOD have been estimated to range between 67 and 81 per 100,000 inhabitants in the 45–64 age group [4]. In a study carried out in the London (neighborhoods of Kensington, Chelsea, Westminster, and Hillingdon), the prevalence of dementia in the 30–64 age group was 54.0 per 100,000 inhabitants (95% CI 45.1–64.1) based on a total population of 567,500 [5]. This prevalence was higher in those aged 45–64 years, with a prevalence rate of 98.1 per 100,000 (95% CI 81.1–118.0). Interestingly, they found a slightly higher prevalence in men in the overall population aged 30–64 years with prevalence rates of 62.6 and 45.5 per 100,000 in men and women, respectively. Conversely, a higher difference was found in the 45–64 age group with prevalence rates of 119.8 and 76.5 per 100,000 in men and women, respectively (**Table 1**) [5].

Population			All causes of dementia									
			All			Male			Female			
Age range	Male (n)	Female (n)	n	Rate*	95% CI	n	Rate	95% CI	n	Rate	95% CI	Significance†
30–34	23898	23375	6	12.7	(4.7 to 26.7)‡	3	12.6	(2.6 to 36.7)	3	12.8	(2.7 to 37.5)	NS
35–39	18526	19106	3	8.0	(1.6 to 23.3)	1	5.4	(0.1 to 30.1)	2	10.5	(1.3 to 37.8)	NS
40–44	18982	19643	6	15.5	(5.7 to 33.8)	1	5.3	(0.1 to 29.4)	5	25.5	(8.3 to 59.4)	NS
45–49	16549	16799	11	33.0	(16.5 to 59.0)	6	36.3	(13.3 to 78.9)	5	29.8	(9.7 to 69.5)	NS
50–54	15185	15237	19	62.5	(37.6 to 97.5)	10	65.9	(31.6 to 121)	9	59.1	(27 to 112)	NS
55–59	13983	13626	42	152.1	(110 to 206)	28	200.2	(133 to 289)	14	102.7	(56.2 to 172)	NS
60–64	12716	13141	43	166.3	(120 to 224)	26	204.5	(134 to 300)	17	129.4	(75.4 to 207)	NS
30–64	119839	120927	130	54.0	(45.1 to 64.1)	75	62.6	(49.2 to 78.4)	55	45.5	(34.3 to 59.2)	NS
45–64	58433	58803	115	98.1	(81.1 to 118)	70	119.8	(93.4 to 151.0)	45	76.5	(55.8 to 102)	NS
Over 65§			55			33			22			

*Rate per 100 000 people at risk.
†Significance of difference between genders by inference from 95% CI.
‡95% confidence interval for the prevalence rate.
§Subjects who had a dementia starting before the age of 65 years, but were over 65 but still living on the study census day.

Table 1. *Age and sex specific prevalence rate in the UK study. Adapted from [5].*

	Alzheimer's disease			Vascular dementia			Frontotemporal dementia			Alcohol related dementia		
Age range	n	Rate*	95% CI	n	Rate*	95% CI	n	Rate*	95% CI	n	Rate	95% CI
40–44	1	2.6	(0.7 to 14.4)									
45–49	2	6.0	(0.7 to 21.7)				4	12.0	(3.3 to 30.7)	2	6.0	(0.7 to 21.7)
50–54	5	16.4	(5.3 to 38.4)	2	6.6	(0.8 to 24.4)	1	3.3	(0.8 to 18.3)	6	19.7	(7.2 to 42.9)
55–59	14	50.7	(27.7 to 85.1)	9	32.6	(14.9 to 67.9)	7	25.4	(10.2 to 52.2)	5	18.1	(5.9 to 42.3)
60–64	20	77.3	(47.2 to 119)	10	38.7	(18.5 to 71.1)	6	23.2	(8.5 to 50.5)	3	11.6	(2.4 to 33.9)
30–64	42	17.4	(12.6 to 23.6)	21	8.7	(5.4 to 13.3)	18	7.5	(4.4 to 11.8)	16	6.6	(3.8 to 10.8)
45–64	41	35.0	(25.1 to 47.4)	21	17.9	(11.1 to 27.4)	18	15.4	(9.1 to 24.3)	16	13.6	(7.8 to 22.2)

*Rate per 100 000 people at risk.

Table 2. *Age specific prevalence rates for EOD according the four main common causes. Adapted from [5].*

In this UK study, the four main common causes of EOD were Alzheimer's dementia (AD), vascular dementia (VaD), frontotemporal dementia (FTD), and alcohol related dementia as showed

in **Table 2**. Another UK study found similar rate with a total of 108 EOD subjects and a prevalence of 81/100,000 (95% CI 62.8–104.5) in the 45–64 age group [6]. In a study carried out in Japan in 2009 collecting EOD cases from various geographical areas, a prevalence rate of 42.3/100,000 (95% CI 39.4–45.4) was found in the 20–64 age group, with higher values in those aged 45–65 years was 83.3/100,000 (95% CI 77.4–89.6) [7]. An Australian study found an overall prevalence of 68.2/100,000 (95% CI 54.9–83.4) considering the overall 30–64 age group, with lower values at younger ages. The prevalence rate was 11.6/100,000 (95% CI 5.3–21.7) and 132.9/ 100,000 (95% CI 105.8–164.2) for the 30–44 and 45–64 age group, respectively [8]. In a study carried out in Brescia province in Italy, it turned out that the prevalence of neurodegenerative dementia was 55.2 per 100,000 inhabitants in the age group 45–65, with no difference between male and female individuals [9]. Finally, recent data from Modena province where this project has been carried out, it turned out an EOD prevalence rate of 74.30/100,000 (95% CI 71.45–77.16) in the overall range group 30–64 years, with values of 3.69/100,000 (95% CI 2.67–4.71) in the age group 30–44 years and 119.85/100,000 (95% IC 115.20–124.49) in the age group 45–64 years, respectively [10]. **Table 3** shows the 5-year specific prevalence rates indicating that prevalence rate increase with the increasing age of population [10].

	Prevalent cases at June 30, 2019			Age and sex specific prevalence at June 30, 2019 (per 100.000 inhabitants)		
Age range (year)	Total	M	F	Total	M	F
30-34	0	0	0	0	0	0
35-39	1	0	1	2.3	0	4.6
40-44	4	1	3	7.4	3.7	11.1
45-49	10	7	3	16.9	23.5	10.2
50-54	29	11	18	50.8	38.4	63.2
55-59	84	44	40	164.5	177.1	152.5
60-64	130	60	70	296.4	285.3	306.7

***Table 3**. Prevalence of all-cause EOD at census date by range of age at onset and sex. Adapted from [10].*

As regards EOD incidence, a study carried out in Norway turned out a value of 14.8 cases per 100,000 person-years for the 30–64 age group and of 25.0 cases per 100,000 person-years in the 45–64 age group, respectively [11]. Similar data were also found in a Spanish study, with an incidence rate of EOD for the age group 30–64 of 13.4 cases per 100,000 person-years [12]. Data from Modena province shows an annual incidence rate of 13.2 new cases per 100,000 in the age groups 30–64 years, with values of 2.94/100,000 (95% CI 2.81–3.07) and 22.06/100,000 (95% CI 21.96–22.15) in the 30–44 and 45–64 age group, respectively [10]. For both prevalence and incidence, AD is the most common diagnosis of EOD, followed by FTD spectrum as shown in **Table 4** [10].

Clinical subtypes	Prevalent clinical subtypes N (%)	Prevalence on June 30, 2019	Incident clinical subtypes N (%)	Incidence (January 1, 2016-June 30, 2019)
AD	113 (100)	32.6	61 (100)	5.0
Amnestic	77 (68.1)	22.2	45 (73.8)	3.7
Posterior cortical atrophy (PCA)	8 (7.1)	2.3	2 (3.3)	0.16
Logopenic variant (lvPPA)	20 (17.8)	5.8	10 (16.4)	0.8
Behavioral/dysexecutive	4 (3.5)	1.2	/	/
NOS	4 (3.5)	1.2	4 (6.5)	0.3
FTD SPECTRUM	78 (100)	22.5	52 (100)	4.3
Behavioral variant (bvFTD)	49 (62.8)	14.1	32 (61.5)	2.6
Semantic variant (svPPA)	11 (14.1)	3.2	9 (17.3)	0.74
Non-fluent primary progressive aphasia (nfvPPA)	2 (2.6)	0.6	2 (3.8)	0.16
FTD-ALS	6[a] (7.7)	1.7	4[b] (7.7)	0.32
Corticobasal syndrome (CBS)	5 (6.4)	1.4	2 (3.8)	0.16
Progressive supranuclear palsy (PSP)	4 (5.1)	1.2	3 (5.9)	0.25
NOS	1 (1.3)	0.3	/	/

N, number of subjects.
NOS, not otherwise specified.
[a] N = 4 bvFTD and N = 2 nfvPPA variants.
[b] N = 3 bvFTD and N = 1 nfvPPA variants.

Table 4. *Alzheimer's dementia and frontotemporal dementia spectrum presentations. Adapted from* [10].

Diagnosis

Time from onset of symptoms and final diagnosis is generally longer for people with EOD compared with LOD [13]. Family and caregivers often complain about this delay due to misdiagnosis caused by clinician's lack of knowledge of the specific EOD features and difficulties in accessing specialist services [14]. Indeed, the diagnosis of EOD is challenging because of the diversity of EOD symptoms: depression is the most common non-dementia diagnosis in young subjects according to data of examination at memory disorder clinics and one study reported that it accounted for over 24% of clinical presentations [15]. Even mild cognitive impairment (MCI) presenting before the age of 65 is a common diagnosis in memory clinics. The annual rate of dementia conversion of MCI subjects attending memory disorder clinics is 15–20% and before dementia could be diagnosed there can be a long prodrome [14]. In an Australian study regarding the delay in diagnosis in EOD and its determinants, it turned out that participants did not sought for a clinical opinion about their symptoms for an average of 2.3 years (median 15 months) [14]. A previous study carried out in LOD found that the average time to first examination is shorter (1.9 years) with still high average time from symptom onset to final diagnosis of 3.1 years [16]. According to the Australian study, different factors predict such longer time from initial dementia diagnosis to final diagnosis of the dementia

type which vary according to the stage of the diagnostic process, clinical features and type of dementia [14].

More recent studies indicate that the mean time from symptom onset and diagnosis is 4.4 years in younger people for all-cause dementia compared with 2.2 years for LOD of comparable severity [17]. In part, this delay is explained by patients and family members not considering the possibility of dementia at a young age. Even when undergone to clinical assessment, EOD is often misdiagnosed for a several reasons. Firstly, clinicians are more familiar with LOD and are less likely to consider a diagnosis of dementia in young subjects. In addition, EOD has a broader differential diagnosis compared to LOD. Changes in personality, behavior, and cognition are often referred to mood disorders such as depression or anxiety. As a consequence, the distinction between neurologic and psychiatric diseases in this age group is challenging, and there is considerable overlap due to common neuroanatomy and neurochemistry features [4].

In **Table 5**, a summary of characteristics of different conditions related to dementia which may help to improve EOD diagnosis is presented, although it especially focus on AD diagnosis [2]. It should be noted that early criteria for AD had low specificity and could be used only to diagnose later during the progression of the disease. Attempts to refine and accelerate diagnosis included the identification of amnestic MCI as a precursor of AD. However, transition from MCI to AD remained still poorly defined. As a consequence, recently published criteria added the use of biomarkers in diagnosis of both MCI and AD, reflecting changes in clinical practice. In particular, in the first column of **Table 5**, there are criteria for amnestic MCI that should not be categorized as having dementia but are important because these have some value in helping to identify precursor states of specific dementia syndromes. The second column presents dementia criteria according to DSM-IV-TR. The third one contains diagnostic criteria for AD from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), which first require that the patient fulfils the criteria for dementia. Thus, before a patient with AD may be diagnosed using these criteria, the disease will be well advanced. Therefore, in the last column have been proposed other criteria for AD that consider both the importance of early diagnosis and the role of biomarkers irrespective of severity.

	Amnestic MCI	Dementia DSM-IV-TR	Alzheimer's dementia NINCDS-ADRDA	Alzheimer's dementia*
History				
Age	NA	NA	40–90 years	NA
Progression	NA	Yes	Yes	Yes
Onset	NA	Gradual	Gradual	Gradual
Memory complaint	Yes	Yes	Yes	Core: early and significant >6 months
Activities of daily living	Normal	Impaired	Impaired	NA
Other CNS/general conditions	NA	Absent	Absent	Absent
Incoordination/gait disturbance	NA	NA	Absent	Absent
Early seizures	NA	. .	Absent	Absent
Examination				
Memory impairment	Core	Core	Core	Core: can be isolated
General cognitive function	Normal	One or more of: aphasia, apraxia, agnosia, disturbance in executive function	Deficits in at least two areas of cognition	Can be intact or deficits in areas of cognition other than memory
Delirium	NA	Absent	Absent	. .
General neurological function	NA	NA	Normal	Normal
Investigation				
MRI	NA	NA	NA	Medial temporal lobe atrophy
CSF	NA	NA	NA	Low amyloid, increased tau or phosphorylated tau
PET	NA	NA	NA	Bilateral temporoparietal hypometabolism on FDG-PET or abnormal PiB study
Genetics	NA	NA	NA	Proven FAD mutation in immediate family

Table 5. Summary of characteristics of different conditions related to dementia. Abbreviations: MCI=mild cognitive impairment. DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision. NINCDS=National Institute of Neurological and Communicative Disorders and Stroke. ADRDA=Alzheimer's Disease and Related Disorders Association. PiB=Pittsburgh B compound. FDG=fluorodeoxyglucose. FAD=familial Alzheimer's dementia. core=core features. NA=not addressed in that set of criteria. *Probable Alzheimer's dementia=core memory impairment plus one or more supportive investigations.

Clinical assessment

The first step for an accurate EOD diagnosis is performing a thorough clinical assessment. This involves obtaining a complete clinical history including symptoms in all cognitive domains and not only memory: behavioral features and psychiatric history, degree of functional impairment, temporal profile of modality of onset and progression of symptoms, past medical history, social history including educational and occupational attainment, and family history of neuropsychiatric disorders. Other relevant features include specific risk factors for dementia including head injury with loss of consciousness or alcohol/drug exposure. It is extremely relevant to assess a collateral history from a reliable informant, as patients may have little insight of their deficits and often forget historical details which are not considered relevant but still important for the final diagnosis [4].

Cognitive assessment

Patients with cognitive impairment should undergo a careful mental status examination. Cognitive and behavioral assessments are tailored to distinguish normal and abnormal performance arising across a range of different conditions. A widely implemented screening tool for cognition is the Mini-Mental State Examination (MMSE), which includes an extended mental status examination (**Figure 1**) [18]. In detail, MMSE is a short standardized form implemented for a serial testing of the cognitive mental state in patients on a neurogeriatric ward, as well as for admission to a hospital. The MMSE was found to be quick to be administrated (5–10 minutes), easy to use due to the low number of questions (n=11), and acceptable for both patients and testers [19]. In 14 studies, the MMSE demonstrated a sensitivity of 88.3% (95% CI 81.3%–92.9%) and a specificity of 86.2% (95% CI, 81.8%–89.7%) for dementia, with a score cutoff of 23 to 25 indicating significant impairment. A meta-analysis of 108 cohort studies reported a sensitivity of 81% (95% CI 78%–84%) and specificity of 89% (95% CI 87%–91%) [20]. Despite the MMSE is commonly used, it turned out that it lacks in sensitivity in the early stages of dementia and does not sufficiently test some cognitive domains, such as executive functions [21]. For this reason, an extended mental status examination including more detailed assessments and observations regarding a broader range of cognition and behavior as well as a longer (30–60 minutes) administration time, should be implemented. The overall pattern of performance helps to identify which brain regions are dysfunctional and provides relevant clues regarding underlying neuropathology [22].

The second type of important examination is a formal neuropsychological testing. Formal neuropsychological testing typically requires several hours to complete because it comprehensively examines multiple cognitive domains to provide a detailed assessment of the nature and severity of cognitive impairments. Despite this difficulty, however, this information can be of high contribution when during investigation of primary and secondary diagnoses and the subsequent implementation of an individualized rehabilitation and treatment. Neuropsychological tests evaluate functioning in

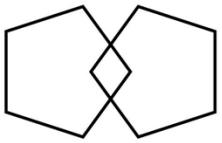
several areas including intelligence, executive functions (such as planning, abstraction, conceptualization), attention, memory, language, perception, sensorimotor functions, motivation, mood state and emotion, quality of life, and personality styles (**Figure 2**) [23].

MINI MENTAL STATE EXAMINATION (MMSE)

Name:

DOB:

Hospital Number:

One point for each answer	DATE:		
ORIENTATION Year Season Month Date Time	...../ 5	...../ 5	...../ 5
Country Town District Hospital Ward/Floor	...../ 5	...../ 5	...../ 5
REGISTRATION Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).	...../ 3	...../ 3	...../ 3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell "WORLD" backwards: DLROW).	...../ 5	...../ 5	...../ 5
RECALL Ask for the names of the three objects learned earlier.	...../ 3	...../ 3	...../ 3
LANGUAGE Name two objects (e.g. pen, watch).	...../ 2	...../ 2	...../ 2
Repeat "No ifs, ands, or buts".	...../ 1	...../ 1	...../ 1
Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear").	...../ 3	...../ 3	...../ 3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".	...../ 1	...../ 1	...../ 1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.	...../ 1	...../ 1	...../ 1
COPYING: Ask the patient to copy a pair of intersecting pentagons 	...../ 1	...../ 1	...../ 1
	TOTAL: ...../ 30	...../ 30	...../ 30

MMSE scoring
24-30: no cognitive impairment
18-23: mild cognitive impairment
0-17: severe cognitive impairment

OME Oxford Medical Education

Figure 1. *Mini Mental State Examination. Adapted from [18].*

Common Neuropsychological Tests by Domain

Domain	Tests
Academic achievement	Wide Range Achievement Test Woodcock-Johnson Tests of Achievement
Adaptive/functional living	Independent Living Scales Vineland Adaptive Behavior Scales
Attention and working memory	Digit span Letter-number sequencing
Emotional functioning/personality	Minnesota Multiphasic Personality Inventory Personality Assessment Inventory
Executive functioning	Stroop task Trail Making Test Wisconsin Card Sorting Test
Intelligence	Wechsler Abbreviated Scale of Intelligence Wechsler Adult Intelligence Scale
Memory	California Verbal Learning Test Rey Auditory Verbal Learning Test Wechsler Memory Scale
Mental processing speed	Digit Symbol-Coding Symbol Search
Premorbid estimation	National Adult Reading Test Test of Premorbid Functioning
Psychomotor functioning	Grip strength test Grooved Pegboard Test
Validity	Test of Memory Malingering Word Memory Test
Verbal functions	Boston Naming Test Controlled Oral Word Association Test
Visuospatial functions	Block design test Rey Complex Figure Test and Recognition Trial
Multidomain test batteries	Neuropsychological Assessment Battery Repeatable Battery for the Assessment of Neuropsychological Status

Figure 2. *Common neuropsychological tests by domain. Adapted from [23].*

Behavioral assessment

Atypical presentations of EOD frequently overlap with psychiatric conditions resulting in misdiagnosis with a psychiatric disease [17]. The behavioral examination begins during assessment of patient's history, with an assessment of the patient's bearing, the interactions with others, and the spontaneous conversation. This assessment is particularly important in subjects who might not have deficits on formal cognitive as for example in the case of behavioral variant of FTD. The approach to testing might also be informative, e.g. it can be impulsive in frontal cortical syndromes, whilst it is slow in subcortical ones. Conversely, patients with AD generally have a well preserved social appearance but may appear passive during the interview, often asking help to their partner to answer questions (the so-called "head turning" sign). In addition to the close observation of the subject, it is important to record a history of behavioral and psychiatric (including major mood or psychotic) symptoms, emphasizing the need for a corroborating history from an informant who knows the patient well [2].

Neurological examination

The additional neurological features of a dementia plus syndrome are generally mild. Therefore, a comprehensive clinical examination is important to narrow the large range of potential underlying pathological changes (e.g., ataxia, pyramidal signs, dystonia/chorea, akinetic-rigid syndrome, peripheral neuropathy). The range and speed of pursuit and saccadic eye movements can be useful in the differential diagnosis (e.g., to identify the supranuclear gaze palsy of progressive supranuclear palsy, Niemann Pick type C disease, and Gaucher's disease). The presence of a jaw jerk or pout, brisk tendon reflexes, and gait apraxia may indicate an underlying vascular disorder. Fasciculations, possible clues of lower motor neuron involvement in some types of FTD, can be restricted to the deltoids and triceps in the absence of long tract signs. Fine myoclonus of the hands in familial AD might emerge only when the patient is relaxed or distracted [2].

Laboratory investigations

Blood tests

Routine hematological and biochemical blood tests are useful for the investigation of comorbidities instead of establishment of the underlying cause [2]. However, they can be helpful in the diagnosis of toxic/metabolic encephalopathies as well as underlying infectious diseases such as HIV or syphilis, and autoimmune illnesses causing impairment also of cognition (see more details below) [24].

Neurogenetics

The need of genetic testing depends on a variety of factors and should be highly tailored on characteristics of subject, including age and presence of additional family members who might be at risk. Among the neurodegenerative dementias, genetic testing is most often pursued for CADASIL, Huntington disease, autosomal-dominant forms of AD and patients with FTD [25-28].

Neuroimaging

Magnetic resonance imaging (MRI) of the brain is an important component of the initial evaluation of suspected EOD. Indeed, MRI improves the diagnosis of dementia as it offers the ability to improve the ante-mortem prediction of pathologic entities through several mechanisms. In AD, MRI allows to assess temporal atrophy (especially in the hippocampus), as well as parietal and prefrontal atrophy. In vascular dementia the typical MRI signs are nonlacunar infarcts, lacunes of possible vascular origin, white matter hyperintensities, microbleeds, perivascular spaces, white matter lesions or superficial siderosis. In the FTD, it is possible to assess prefrontal and anterior temporal atrophy [29]. In Creutzfeldt-Jakob Disease (CJD), characteristic features on MRI have been identified, with differences across the several forms of CJD: sporadic Creutzfeldt-Jakob Disease (sCJD) may be associated with high signal changes in the putamen and caudate head while variant Creutzfeldt-Jakob Disease (vCJD) is usually associated with hyperintensity of the pulvinar of the thalamus, particularly the posterior nuclei [30].

Cerebrospinal fluid (CSF)

Examination of the CSF is useful to identify inflammatory causes such as multiple sclerosis, vasculitides, and infections. Along with polymerase chain reaction (PCR), CSF analysis may help to identify specific chronic infections such as subacute sclerosing panencephalitis, infection of *human herpesvirus 6*, cryptococcosis, tuberculosis or Whipple's disease. The assessment of specific proteins can be diagnostic for particular neurodegenerative diseases: presence of 14-3-3 protein in the CSF is suggestive for the diagnosis of CJD and forms part of diagnostic guidelines for dementia; CJD is also characterized by high levels of CSF tau protein. Decreased amyloid β and increased tau levels demonstrated good sensitivity and specificity for AD and therefore have been incorporated into recent diagnostic criteria for its diagnosis [2].

Tissue biopsies

Brain biopsies is reserved for cases where all diagnostic tests have been implemented but failed to identify a cause. In addition, in highly specific cases, a less invasive tissue biopsies can be of added value in a number of diagnoses such as skin in CADASIL or muscle in mitochondrial cytopathies. Tonsillar biopsy can provide a definitive diagnosis in nvCJD [4].

Causes of early onset dementia

Figure 3 shows an overview of main causes of EOD assessed in detail below.

Neurodegenerative dementias
Alzheimer disease
Presenilin 1 mutation
Presenilin 2 mutation
Amyloid precursor protein mutation
APOE ε4-associated disease
Down syndrome related dementia
Frontotemporal dementia
Dementia with Lewy bodies
Parkinson disease dementia
Progressive supranuclear palsy
Corticobasal degeneration
Multiple system atrophy
Vascular diseases
Vascular dementia
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Cerebral amyloid angiopathy
Primary angiitis of the central nervous system
Secondary central nervous system vasculitis
Infectious diseases
Prion disease
HIV-associated neurocognitive disorder
Herpes encephalitis
Neurosyphilis
Whipple disease
Progressive multifocal leukoencephalopathy
Subacute sclerosing panencephalitis
Inflammatory and autoimmune diseases
Multiple sclerosis
Neurosarcoidosis
Paraneoplastic encephalopathy
Non-paraneoplastic autoimmune encephalopathy
Encephalopathy due to systemic autoimmune disease
Neurometabolic disorders
Mitochondrial disease
Late-onset lysosomal storage diseases
Adult-onset leukodystrophies
Adult polyglucosan body disease
Diffuse hereditary leukoencephalopathy with axonal spheroids
Adult neuronal ceroid lipofuscinosis
Others
Chronic traumatic encephalopathy
Alcohol-related dementia
Normal pressure hydrocephalus
Huntington disease
Wilson disease
Spinocerebellar atrophy
Dentatorubral pallidoluysian atrophy
Familial encephalopathy with neuroserpin inclusion bodies
Pantothenate kinase associated neurodegeneration
Familial idiopathic basal ganglia calcification (Fahr disease)
Superficial siderosis

Figure 3. *Causes of early onset dementia. Adapted from [31].*

Neurodegenerative dementias

AD, vascular dementia, FTD, and dementia with Lewy bodies are the most common diseases that cause neurodegenerative dementia as shown in the distribution presented in **Figure 4** [2].

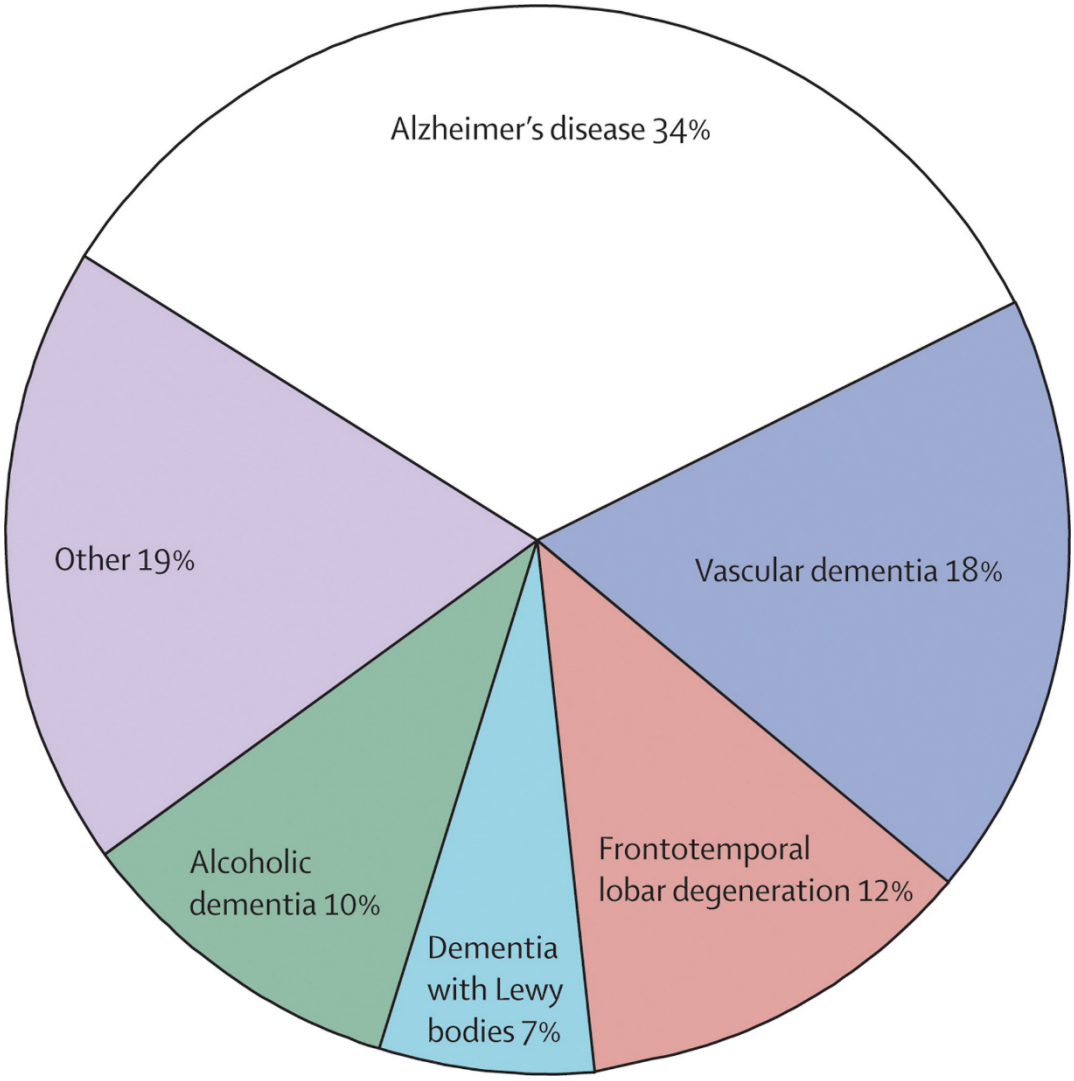


Figure 4. *Epidemiology of early onset dementia. Adapted from [2].*

This distribution is also confirmed in the investigated area of Modena province, where a substantial comparable distribution of EOD diagnosis was recently found as AD and FTD spectrum are the most frequent diagnoses in prevalent cases (**Table 6** and **Figure 5**).

Clinical diagnosis	N	%	M/F
Total	258	100	123/135
AD	113	43.8	36/77
FTD spectrum	78	30.2	44/34
Vascular dementia	24	9.3	16/8
Lewy body dementia	9	3.5	5/4
Leukoencephalopathy	7	2.7	5/2
Parkinson disease dementia	7	2.7	6/1
Alcoholic dementia	4	1.5	3/1
Cerebral amyloid angiopathy	3	1.2	2/1
Dementia in Huntington disease	3	1.2	2/1
NOS	10	3.9	4/6

AD, Alzheimer's dementia; FTD, frontotemporal dementia; NOS, dementia not otherwise specified.

***Table 6**. Clinical diagnosis of prevalent cases in Modena province. Adapted from [10].*

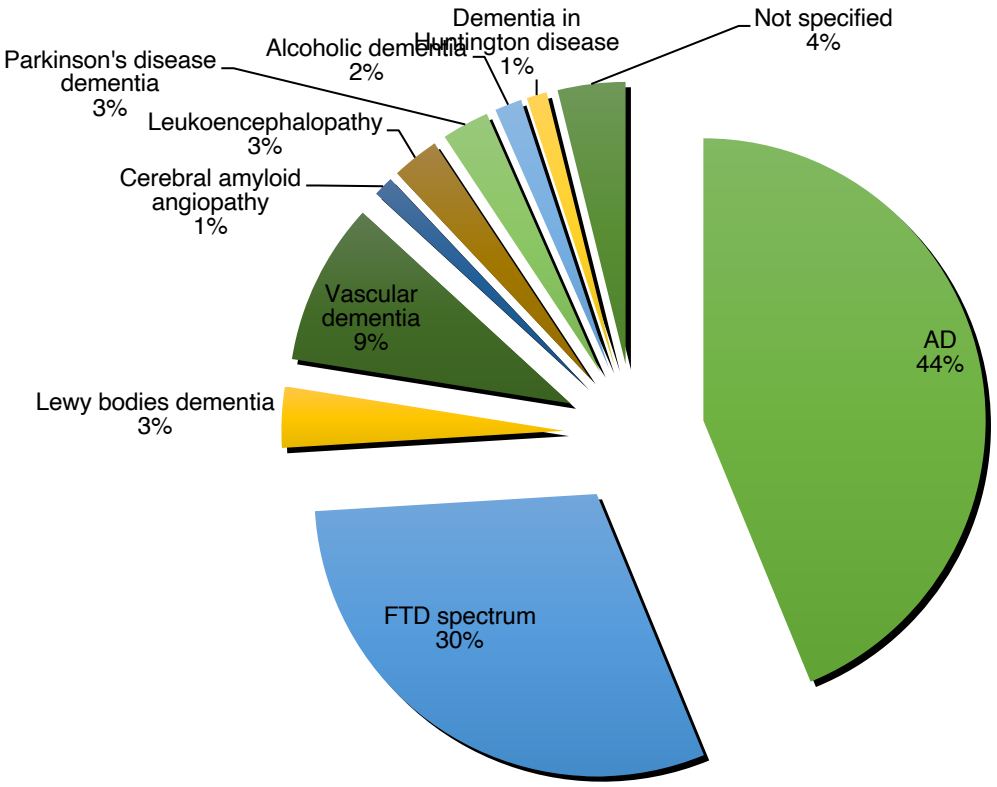


***Figure 5.** Distribution of EOD diagnosis in Modena Province. Data from [10].*

Alzheimer's dementia (AD)

Alzheimer's dementia in younger adults is most often the sporadic form, but in those with a family history of EOD, dominantly inherited genetic mutations are common including the following:

- *Presenilin 1 (PSEN1)*: causative mutations in *PSEN1* are the most common genetically confirmed cause of familial AD with early onset, accounting for over 50% of cases. Mutations are fully penetrant, with a median age of onset of 43 years [25]. Inheritance of mutations in *PSEN1* gene may be associated with a higher prevalence of other neurological signs which anticipate the development of cognitive deficits. This is particularly true in subjects with disease onset before 40 years [32]. *PSEN1* mutation carriers more frequently present atypical cognitive symptoms and additional neurological features. Behavioral, language, and dysexecutive manifestations, spastic paraparesis, and other pyramidal, extrapyramidal, and cerebellar signs have been described [33].
- *Presenilin 2 (PSEN2):* mutations in the *PSEN2* gene found on chromosome 1q are a much rare cause of familial AD with early onset. Although PSEN2 has high homology with PSEN1 (≥60%), its mutations are estimated to be not fully (95%) penetrant, and the median age of onset occurs generally later and in a more variable way than with other mutations [34].
- *Amyloid precursor protein (APP)*: *APP* mutations account for up to 15% of genetically confirmed cases of familial AD with early onset. Causative mutations in *APP* are fully penetrant. Considering that *APP* gene is on chromosome 21, people with Down syndrome are at higher risk of AD, which frequently emerges in the fifth decade, due to 1.5 *APP* gene dose [35].
- *Apolipoprotein ε4 (APO ε4):* in sporadic AD, certain genetic polymorphisms have been associated with increased disease risk, most notably and powerfully the *APOE* ε4 allele. Particularly when inheritance is homozygous, *APOE* ε4 increases risk of AD and lowers the age of onset compared with those without the ε4 allele. Homozygous inheritance of *APOE ε4* gene is generally associated with onset of cognitive changes before 65 years [36, 37].

Frontotemporal dementia (FTD)

FTD is a group of clinically and neuropathological heterogeneous neurodegenerative disorders characterized by prominent changes in social behavior and personality or aphasia linked to the degeneration of the frontal and/or temporal lobes. FTD is the second most common cause of dementia in people with less than 65 years. The mean age of onset is between 45 and 65 but there have been described cases younger than age 30 and also in the elderly. FTD is likely underdiagnosed especially in case of non-neurologist examination due to the lack of recognition and the overlap with a variety of psychiatric disorders considering the specific behavioral features [38].

Neurodegenerative disease associated with tau protein

Neurodegenerative diseases associated with abnormal accumulation of tau protein include clinical phenotypes ranging from certain variants of FTD to corticobasal syndrome and progressive supranuclear palsy. Most of these entities start with cognitive and behavioral changes, typically before 65 years, accompanied by additional signs and symptoms of impairment of motor neuron. Many of these diseases show overlap in both pathology and clinical phenotype [39].

Dementia with Lewy bodies (DLB)

Dementia with Lewy bodies represents a less common cause of EOD. The average age at onset of DLB is 75 years, although cases with early onset are increasing. Most DLB cases are sporadic. In addition to cognitive dysfunction, core clinical features are cognitive fluctuations, visual hallucinations, and Parkinsonism. Rapid eye movement (REM) sleep behavior disorder is also a common sign of DLB. Genetic associations have been recognized in several studies including duplication or triplication of alpha-synuclein gene, mutation of glucocerebrosidase, gamma-synuclein and potentially presenilin gene mutations [40].

Parkinson's disease (PD) dementia

PD is a possible cause of EOD. The risk of developing dementia in these patients is 5.1 times higher. Higher and increasing age, the later age of onset of PD, the longer duration of symptoms, the presence of hallucinations, and the impairment of memory and language functions were all predictive factors for the development of dementia. [41] Despite the majority of PD cases appear to be sporadic, monogenetic forms of PD are increasingly recognized, involving often early or severe cognitive changes. PD has been associated with mutations in glucocerebrosidase gene as well as of forms of alpha-synuclein gene [42].

Vascular diseases

Cerebrovascular and cardiovascular diseases cause vascular brain injury which can lead to cognitive impairment Vascular cognitive impairment is considered the second most common neuropathology of dementia and MCI, accounting for up to one-third of the population risk [43]. Geographical variations have also been described, as for example in Japan where the prevalence of vascular dementia is higher than AD [7].

Vascular dementia is generally divided into two clinical forms [43]:

- a clinically diagnosed stroke is followed by onset of dementia symptoms; or
- vascular brain injury identified with brain imaging techniques in subjects with cognitive decline but in absence of a medical history of stroke.

Vascular dementia may be caused by any cerebrovascular or cardiovascular disease that leads to vascular brain injury or dysfunction, including any ischemic (either cardioembolism, cerebral small vessel disease or large artery atherosclerotic disease) or hemorrhagic stroke. The diagnosis of vascular dementia cannot be established without the identification of the underlying cerebrovascular or cardiovascular diseases. This information is necessary to implement a plan for secondary prevention of future vascular brain injury.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant disease caused by mutations in the *NOTCH3* gene on chromosome 19. CADASIL is therefore and inherited angiopathy with major clinical manifestations characterized by transient ischemic attack and ischemic stroke, cognitive deficits with early executive dysfunction, migraine with aura, and neuropsychiatric disturbances. Increasing subcortical infarct burden tends to cause EOD within 50–60 years [44].

Cerebral amyloid angiopathy (CAA)

Cerebral amyloid angiopathy (CAA) is characterized by deposition of amyloid β peptide within small to medium-sized blood vessels of both brain parenchyma and leptomeninges. Despite CAA is generally asymptomatic, it may be associated with primary lobar intracerebral hemorrhage in older subjects. [45] In addition to intracerebral hemorrhage, CAA may be characterized by with transient neurological symptoms, inflammatory leukoencephalopathy, or incidental microbleeds or hemosiderosis identified with MRI investigation. The incidence of CAA is strongly age dependent like AD. A study carried out in 784 autoptic investigations estimated a prevalence from moderate to severe CAA as 2.3% for patients between 65 and 74 years, 8.0 % between 75 and 84 years, and 12.1% over 85 years [46].

Primary angiitis of the central nervous system

Primary angiitis of the central nervous system is a rare entity caused by an immune-mediated attack on small and medium blood vessels in the brain, spinal cord, and leptomeninges. Cognitive dysfunction occurs in the majority of subjects. Other features which are common in these subjects are headaches, seizure, stroke, and cerebral hemorrhage. The estimated annual incidence rate of primary angiitis has been estimated in 2.4 cases/1,000,000 person-years [47].

Secondary central nervous system vasculitis

Secondary central nervous system vasculitis may be caused by a variety of vasculitides associated with systemic autoimmune diseases. Also infection can lead to such vasculitis. The forms

of vasculitis most likely to involve the central nervous system are Behçet syndrome, polyarteritis nodosa, vasculitides associated with antineutrophil cytoplasmic antibodies, and cryoglobulinemic vasculitis [48]. *Varicella zoster* virus is an increasingly recognized cause of vasculitis that can affect people at any age in either presence of absence of dermatologic manifestations [49].

Infectious diseases

Prion disease

Prion disease can be acquired, sporadic, or genetic. Creutzfeldt-Jakob disease (CJD) is the most frequent sporadic prion entity, affecting annually approximately 1/1,000,000. Cognitive dysfunction, myoclonus, pyramidal or extrapyramidal dysfunction, visual disturbance and cerebellar signs are the most frequent clinical signs. The mean age of onset of sporadic CJD is 68 years [50]

HIV-associated neurocognitive disorder (HAND)

Many HIV-infected patients eventually develop some form of HAND. In a cohort of 1555 HIV-infected individuals with a mean age of 43 years, 52% had some degree of neuropsychological impairment, and 2% had HIV dementia. [51] Risk factors for the development of HIV dementia include older age, higher immunosuppression prior to beginning of antiretroviral therapy, comorbid infections (especially with hepadnaviridae type B or C), and substance abuse.

Inflammatory and autoimmune diseases

Multiple sclerosis (MS)

Cognitive impairment is a common concomitant symptom of multiple sclerosis (MS) at any stage of the diseases, with a ranging prevalence of 40–70%. MS alters several aspects of cognitive functioning, including attention, information processing efficiency, executive functioning, processing speed and long-term memory, being the latest two features the most common. The areas of cognition which are less affected are attention (e.g., repeating digits) and essential verbal skills (e.g., word naming and comprehension). Despite most studies suggest that general intelligence is not affected in subjects with MS, cognitive intelligence deficits cannot be excluded, with high variation among MS subjects [52]. The degree of such cognitive decline is highly correlated with the severity of cerebral pathology and lesion burden on MRI, including the persistence of T1 black holes, meaning a relevant loss of tissue architecture, and atrophy of the corpus callosum and thalamus. As a matter of that, the amount of cortical atrophy as assessed through MRI investigation is correlated with cognitive changes in MS subjects, suggesting that both gray and white matter atrophy contribute to the clinical occurrence of cognitive decline [53].

Paraneoplastic and autoimmune limbic encephalitis

Paraneoplastic limbic encephalitis is characterized by acute or subacute mood and behavioral changes, short-term memory problems, complex-partial seizures (including faciobrachial dystonic seizures in patients with anti-leucine-rich glioma inactivated 1 antibodies), and cognitive dysfunction. Although several type of cancers can cause paraneoplastic limbic encephalitis, the most common is small cell lung carcinoma. The underlying cancer could be still not identified before the onset of the disease as there are an increasing number of antibody-mediated syndromes recognized in subjects with and without diagnosis of neoplastic disease [54].

Other non-paraneoplastic autoimmune encephalopathies

Autoimmune dementia is a term that has been used to identify an entity which is responsive to steroid-therapy. This autoimmune disorder is characterized by a rapidly progressive dementia with a variable course. This condition, unlike paraneoplastic encephalopathy, is more common in women [54].

Encephalopathy associated with systemic autoimmune disease

Several autoimmune entities such as systemic lupus erythematosus, Sjögren syndrome, Hashimoto's disease and Behçet syndrome have been associated with progressive cognitive impairment. These diseases may cause both immune complex–mediated inflammatory vasculitis and non-vasculitic autoimmune inflammatory meningoencephalitis [55, 56].

Neurometabolic disorders

Mitochondrial diseases

Mitochondrial diseases may have a wide range of clinical presentation with a higher prevalence in younger subjects. The neurologic symptoms which are common in mitochondrial diseases including stroke-like symptoms and encephalopathy consistent with a clinical picture of EOD [57].

Leukodystrophies

Leukodystrophies and genetic leukoencephalopathies are a rare group of entities leading to progressive degeneration of cerebral white matter. They are associated with a spectrum of clinical phenotypes dominated by dementia, psychiatric changes, movement disorders and upper motor neuron signs. They can present in either children or young adults, often with a variety of clinical features including dementia, movement disorders, ataxia and upper motor neuron signs. These diseases are generally accompanied by hyperintense signal alterations in the brain/spinal cord identified on T2-weighted MRI [58].

Adult neuronal ceroid lipofuscinosis (ANCL)

ANCL is a rare inherited neurodegenerative disease characterized by abnormal liposomal accumulation of lipofuscins into neurons. An adult form of NCL, called 'Kufs disease', typically presents cognitive and motor system dysfunction with a very early age of onset, generally around 30 years of age [59].

Chronic traumatic encephalopathy (CTE)

Chronic traumatic encephalopathy (CTE) is a debilitating neurodegenerative disease, which has been increasingly reported especially in athletes, particularly American football players, as well as military veterans, commonly as a result of repetitive mild traumatic brain injuries. CTE has a specific unique neuropathological feature with accumulation of phosphorylated tau (p-tau) in sulci and peri-vascular regions, microgliosis, and astrocytosis. Clinically, CTE is characterized by a subtle clinical presentation, as subjects generally present with two distinct phenotypes: the first subtype initially presents affective changes, while the second subtype is characterized by cognitive impairment. As regards genetic factors, there are no clear genes increasing disease risk, although APOE ε4 carriers have been reported to be much severely affected after traumatic brain injury [60] The most common observed symptoms are memory loss, irritability, outbursts of aggressive or violent behavior, confusion, speech abnormalities, cognitive decline, gait abnormalities, unsteadiness, headaches, slurred speech, and Parkinsonism [61].

Complications of alcohol abuse

Chronic alcohol use can be a cause of neurological dysfunction. This can lead to several clinical forms, including Korsakoff syndrome, Marchiafava-Bignami disease, and cognitive dysfunction with ventricular enlargement. Post-mortem reduction in brain volume and MRI signs of brain damage have been described though possibly multiple pathways are possible. It should be noted that high-level of alcohol intake, i.e. more than 14 drink units per week, has been certainly linked to an increased risk of dementia [62].

Normal pressure hydrocephalus (NPH)

Normal pressure hydrocephalus (NPH) refers to a clinical entity characterized by a pathologically enlargement of ventricular size with normal opening pressures on lumbar puncture. NPH is a form of communicating hydrocephalus and is distinguished from obstructive or non-communicating hydrocephalus, in which there is a structural blockage of the cerebrospinal fluid circulation within the ventricular system, e.g., due to the stenosis of aqueduct of Sylvius. NPH is a rare condition compared with other causes of dementia in older adults with an annual incidence varying in different studies from 2 to 20 per million population. NPH clinical syndrome is associated

with a classic triad of dementia, gait disturbance, and urinary incontinence. The cognitive disturbance of NPH evolves in a long period from months to years and usually develops after the onset of gait dysfunction. Subjects typically have both subcortical and frontal features, including: psychomotor slowing, decreased attention and concentration, impaired executive function and apathy [63].

Wilson disease (WD)

Wilson disease (WD) is an inherited disorder with impairment of copper metabolism resulting in increasing copper levels in the circulation system and toxicity on the hepatocytes. As a result, copper accumulates in several organs, especially the central nervous system. WD occurs worldwide, usually in the age range between 5 and 35 years. Clinical presentations include a combination of hepatic, neurological, ophthalmic and psychiatric features [64]. The majority of neurologic manifestations consist of a movement disorder associated with bulbar symptoms. The movement disorder is usually characterized by tremor, dystonia or Parkinsonism, with generally a subtle onset. Bulbar symptoms usually co-exist and they include dysarthria, drooling and dysphagia. Additional neurological manifestations include cerebellar dysfunction, chorea, hyperreflexia, seizures and cognitive impairment along with psychiatric disorders [65].

Huntington disease (HD)

Huntington disease (HD) is the most common monogenic neurodegenerative disease. HD is an inherited autosomal dominant disease due to repeated expansion of a trinucleotide (cytosine-adenine-guanine-CAG) within the *huntingtin* gene [66]. The dominant cognitive feature of HD is executive dysfunction with decreased ability to make decisions, multi-task, and switch from one set of cognitive goals to another. Subjects typically lack insight into their cognitive deficits, and may be unaware of their perceptual, motor, and psychiatric problems [67].

Differential diagnosis

In summary, there are several non-degenerative diseases which can present with cognitive impairment or in which dementia is the major or only feature. These are diseases that can mimic AD and often present in EOD clinics. It is important to get differential diagnosis because often they can be successfully treated.

Early onset forms of adult neurodegenerative conditions are the most important and frequent forms to be distinguished and recognized and include AD, vascular dementia, FTD, Lewy body dementias, Huntington's disease, and prion disease. Less common late onset forms of childhood neurodegenerative conditions may also present as EOD and include mitochondrial disorders, lysosomal storage disorders, and leukodystrophies. Potentially reversible etiologies including inflammatory disorders, infectious diseases, toxic/metabolic abnormalities, transient epileptic

amnesia, obstructive sleep apnea and normal pressure hydrocephalus also represent important differential diagnostic considerations to treat as soon as possible due to their reversible nature (16). For these reasons, differential diagnosis is extremely important with implementation of a full neurological, instrumental and biomarkers assessment as summarized in **Figure 6** [2].

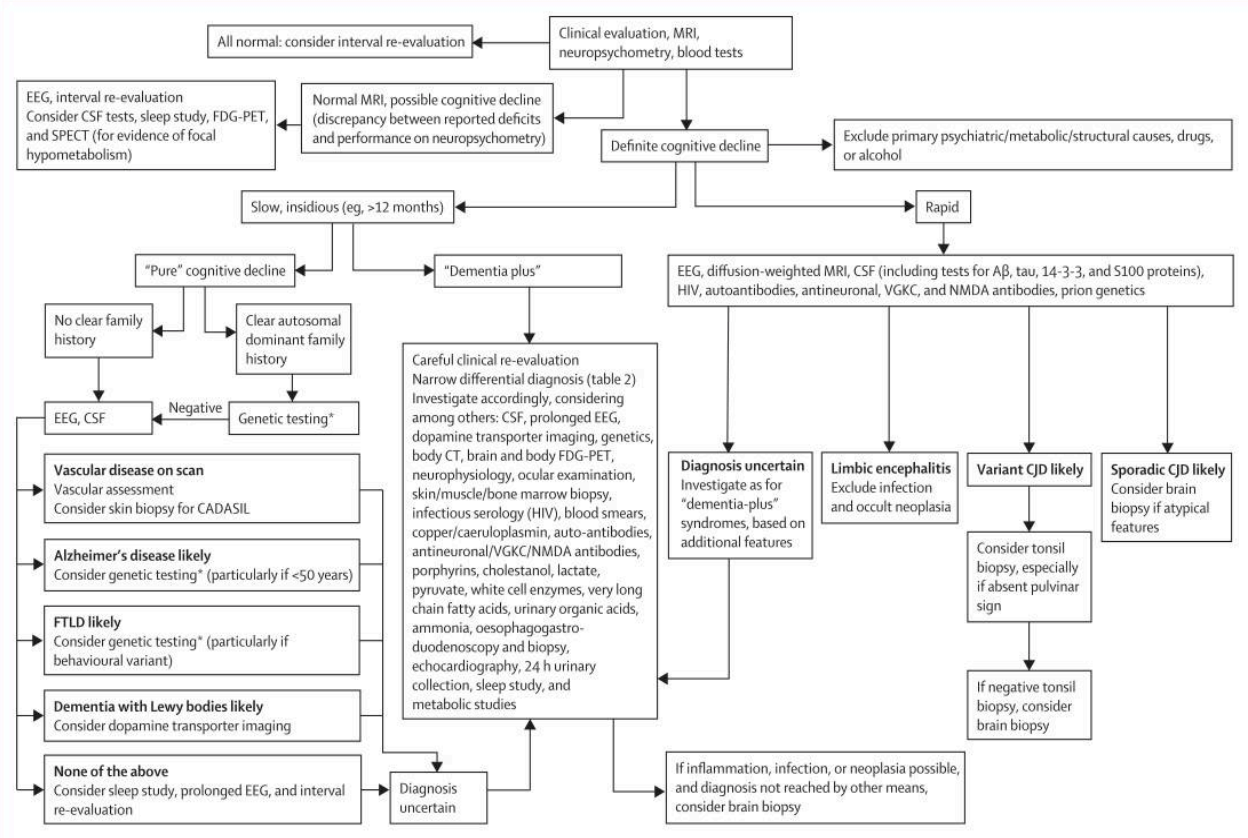


Figure 6. *Flow chart for assessment and investigation of EOD. Adapted from [2].*

Risk factors

EOD does not appear to be a dominantly inherited condition, with more than 70% of patients being sporadic in nature. Furthermore, known mutations were found in less than 10% of the total EOD subjects [68]. The majority of degenerative and vascular EOD cases may therefore be associated with potentially modifiable risk factors, probably interacting with genetic, polymorphic or epigenetic influences [69]. Cardiovascular disease, low education, psychiatric illness, smoking, traumatic brain injury (TBI), physical inactivity and midlife obesity, alcohol use, drug intoxication other than alcohol, hypertension and type II diabetes mellitus (DM) have all been linked to dementia in older people [70]. These risk factors were multiplicative, most of them were potentially modifiable, and most of them could be traced to adolescence, suggesting excellent opportunities for early prevention.

A Swedish study [71] evaluated risk factors in late adolescence for the development of EOD later in life. During a median follow-up of 37 years, 487 men were diagnosed as having EOD at a median age of 54 years. Nine independent risk factors were identified that accounted for most cases of EOD in men. In summary, these factors accounted for 68% of the EOD cases identified. The relevant risk factors that has been identified included alcohol intoxication, stroke, use of antipsychotics, depression, father's dementia, drug intoxication other than alcohol, low cognitive function at conscription, low height at conscription, and high systolic blood pressure at conscription. These risk factors were multiplicative, most of them were potentially modifiable, and most of them could be traced to adolescence, suggesting excellent opportunities for early prevention. Moreover, in the same study a diagnosis of EOD was associated with the second highest risk for death, whereas alcohol intoxication was associated with the highest risk.

About alcohol consumption, study findings also suggest that the risk of very heavy consumption extends to primary degenerative and vascular dementias, and that there was no protective effect of mild to moderate alcohol consumption [72].

An Australian study for the first time studied the impact of non-genetic factors in exclusively non-autosomal dominant primary degenerative and vascular EOD, while eliminating the confounding effect of directly inherited dementias and those occurring secondarily to other diseases [73]. It pointed put the importance of the timing and severity of exposure in influencing risk and also for the first time consider as population the urban Aboriginal Australians, who report EOD at much higher rates than the non-Aboriginal population [74]. In that study a very important role was found for education, a result consistent with other previous studies. Poor educational attainment was particularly detrimental when in combination with a low complexity main lifetime occupation, but some compensation was evident with a high complexity occupation, a finding that that has not been previously explored in EOD groups. The results emphasize the power of early life intellectual enrichment, but also support the possibility of recovery from disadvantage and the benefit of tapping into previously underutilized intellectual potential [73]. Another important finding of that study, consistent with results from LOD studies [75], is even that participation in a range of cognitive leisure activities at least once a month from adolescence to middle age was associated with a three-fold reduction in EOD risk. Furthermore, they are noted to provide benefits even when first implemented late in life or closer in time to the onset of dementia. However, leisure activity was not powerful enough to compensate for low formal educational attainment [73].

Stroke represents an important risk factor, followed by hypertension only when occurring more than 10 years prior to dementia onset, representing an important time dependent effect consistent with the same generally recognized time-dependent effect in LOD.

There was also no effect of hypercholesterolemia or diabetes in the same Australian study [73]. The authors of the study suggest that this difference with LOD risk factors could be due to the

fact that cardiovascular factors are less common in younger groups and are uncommon in those with early onset AD overall. Moreover, evidence also suggests that, among those with neurodegenerative disease, a concurrent cerebrovascular disease is more common with increasing age. It is possible that cardiovascular risk factors require a longer period of exposure to confer risk [73].

In one retrospective cohort study carried out in Sweden it turned out that a lifetime documented diagnosis of depression or anti-depressant use in men increased risk of EOD (Hazard Ratio: 1.89, 95% CI 1.53–2.34) [71]. A Taiwanese retrospective cohort study found a strong relationship between bipolar disorder and dementia (adjusted OR: 4.32, 95% CI 3.21–5.82); moreover, a significantly increased risk was observed in subjects diagnosed with dementia before the age of 65 years (adjusted OR: 3.77, 95% CI 1.78–8.01) [76].

A Japanese recent case-control study demonstrated that use of antidepressant, antipsychotic and antithrombotic drugs was higher amongst patients with AD (19.4%, 34.5% and 11.3%, respectively) than controls (2.9%, 10.3% and 7.3%, respectively) [72]. Moreover, two retrospective cohort studies found an increased risk for EOD with lifetime use of antidiabetic medication [71] and a concurrent diagnosis of diabetes in medical records [72]. While recent studies suggested an association between EOD and diabetes in all patients, but not in male patients specifically [71, 77], the Japanese results suggested that there was no association between AD and diabetes in all patients, although there was a weak association amongst men only. These differences may be yielded by other factors like race of participants or definitions implemented to assess the presence of either AD or diabetes [72].

Regarding smoking habits, it is even possible that smoking confers risk for EOD through its relationship with cardiovascular risk factors like hypertension and stroke [73].

Traumatic brain injury

Accumulating evidences suggest that traumatic brain injury (TBI) is also associated with risk of developing dementia, which is one of the most feared consequences of TBI [78-80]. This represents a leading cause of death and disability in individuals aged <45 years in industrialized countries as neurosurgical and neurological cares allow most victims of even severe injuries to survive for many decades with their disabilities. In young children and elderly individuals, falls were found to be the primary cause of TBI hospitalizations and deaths, while traffic crashes are the primary cause in adolescents and young adults [80, 81]. Similarly, other epidemiological findings indicated that TBI occurred in early to midlife is associated with subsequent 2- to 4-fold increased risk of dementia compared with the general population [80]. Moreover, a recent Swedish study reported that the risk of dementia diagnosis decreases over time after TBI, but it is still evident more than 30 years after the trauma [78]. Such association is stronger in case of occurrence of both severe and

multiple TBIs, with still increased risk after adjustment for familial factors in a time- and dose-dependent manner.

A summary of recent conclusions on the TBI-dementia relationship have been listed [82]: 1) Increasing severity of a single moderate-to-severe TBI increases the risk of subsequent Alzheimer's disease (AD), the most common type of dementia; 2) repetitive, often subconcussive, mild TBIs increases the risk for chronic traumatic encephalopathy; 3) TBI may be a risk factor for other neurodegenerative disorders which can be associated with dementia; 4) TBI appears to lower the age of onset of TBI-related neurocognitive syndromes, potentially adding "TBI cognitive-behavioral features"; 5) specific risk factors for TBI-associated dementia are the occurrence of any blast or blunt physical force to the head as long as there is violent head displacement, the decreased cognitive and/or neuronal reserve and the related variable of older age at TBI; and the presence of APOE ε4 alleles, a genetic risk factor for AD as previously described; 6) neuropathological features relating TBI with neurocognitive syndromes are the presence of amyloid pathology and other neurodegenerative proteinopathies after acute TBI, the occurrence of common features between TBI and CTE, and the disruptions in white matter tract and neural network after TBI.

Nevertheless, some more recent results in contrast with previous ones, suggest that there was no effect of TBI of any kind [73]. The different results are likely related to the very low absolute risk for EOD associated with TBI overall.

Environmental risk factors

The occurrence of geographical variation in dementia rates suggests that environmental risk factors can be relevant factors affecting dementia risk and involved in its pathogenesis. In 2016 a comprehensive systematic review of environmental risk factors for dementia has summarized findings of many and different previous studies [69]; specifically, six categories of risk factors were considered: air quality, toxic heavy metals, other metals, other trace elements, occupational-related exposures, and miscellaneous environmental factors. **Table 7** below is adapted from the review [69] and shows the synthesized evidence from all studies with a global judgement of the strength of such associations.

Factors	N. studies[a]			Overall strength of evidence	Direction of Association[b]
	C	X	R		
Air					
Nitrogen oxides (NO_x)	2			Strong	↑
Carbon monoxide (CO)	1			Moderate	↑
Environmental tobacco smoke		1		Moderate	↑
Particulate matter (PM_{10}&$PM_{2.5}$)	1	1		Strong	↑
Ozone (O_3)	1	1		Strong	↑

Toxic heavy metals					
Arsenic		2		Moderate	↕
Lead		1		Weak	↑
Other metals					
Aluminum	1	15		Moderate	↕
Calcium	1			Weak	–
Cobalt		1		Weak	–
Copper		2	1	Weak	↕
Iron		2	1	Weak	↕
Manganese		1		Weak	↑
Molybdenum		1		Weak	–
Nickel		1		Weak	–
Uranium		1		Weak	–
Zinc		2		Weak	↕
Other trace elements					
Fluoride		1		Weak	↑
Selenium			1	Moderate	↕
Silicon (and silica)	2	2		Strong	↕
Occupational					
Aluminum (occupational exposure)	1	3		Weak	↕
Defoliants/fumigants	1			Weak	↑
Diesel motor exhaust	1			Moderate	–
Electromagnetic fields	1			Moderate	↕
Excessive noise	1			Weak	↓
Glues/adhesives	1	1		Weak	↕
Pesticides/fertilizers/herbicides/insecticides	5	2	2	Strong	↕
Lead (occupational exposure)			1	Weak	–
Metals (occupational exposure)	1			Moderate	↑
Inks/dyes	1			Weak	–
Paints/stains/varnishes	1			Weak	–
Gasoline/fuels/oils	1			Weak	–
Solvents/degreasers	2	1	1	Strong	↕
Liquid plastics/rubbers	1			Weak	–
Vibratory tools	1			Weak	–
Radiation	1			Weak	↑
Miscellaneous					
Climate		1		Weak	–
Electric and magnetic fields	1		2	Moderate	
Mobile phone use	1			Weak	↓
Vitamin D	3	1		Strong	↑
Water pH		1		Weak	↑

Table 7*. Quality of overall evidence for each environmental factor. Adapted [69].* [a]C *cohort studies,* X *cross-sectional studies,* R *reviews. Studies can appear in multiple rows;* [b]*Increased levels of the exposure are associated with:* ↑ *an increased risk of dementia;* ↓ *a decreased risk of dementia;* ↓↑ *mixed results on dementia risk; and-no substantial effect on dementia risk.*

To summarize, according to the results and conclusions of the review, it has been found a moderate evidence that air pollution exposure is related to dementia risk, particularly nitrogen oxides, particulate matter and ozone. Little evidence that toxic heavy metals, or indeed most metals, influence dementia risk, apart from aluminum where larger, better quality studies suggested an association. Other than silicon, there was little evidence for other trace elements affecting dementia risk, though selenium remains an interesting element. Among the occupational exposures, there was in general little evidence, although exposure to some pesticides and, possibly, metals may affect dementia risk. Finally, there was moderate evidence for electromagnetic fields, though this complicated exposure requires some unpicking [69].

Recently, the assessment of the impact of green areas on health has also greatly increased in biomedical and in particular epidemiological research. Several studies highlighted a presence of a positive correlation between exposure to urban greenness and a reduction in blood pressure, cortisol levels, depression, and deaths from all causes [83] and recently also neurodegenerative diseases [84]. Strongly related with greenness exposure, a further element of recent considerable interest in epidemiological research is the exposure to artificial light at night (LAN) which it has been suggested to be a confounding factor for the studies that investigate the relationship between human health and green areas [85]. LAN exposure has been associated with several types of cancer, psychiatric disorders such as depression, bipolar disorder, anxiety disorders, suicidal risk), and metabolic disorders such as obesity [86-88]. The mechanism underlying this possible association could be linked to alterations in the circadian rhythms or more generally to the induction of a stress condition. The reduction of green areas is accompanied by an increase in night luminance, as a consequence of increasing urbanization [85].

As far as the association between LAN and dementia is concerned, human epidemiological studies are still lacking, but some experimental studies on animal models are available. In particular, a study was carried out on *Drosophila melanogaster* exposed to a dim light at night (dLAN) with an intensity of 10 lux (considered as the lower limit of light pollution in many countries), provided interesting results indicating a possible positive association. In the experiment, an AD model of *Drosophila melanogaster* with increased expression of human phosphorylated tau protein was exposed to dLAN. The study pointed out an alteration of the circadian rhythm and sleep disturbances with deposition of tau protein and causing the neurodegeneration in the fly model. The suggested mechanisms involved during the day accumulation in the brain of toxic materials that are normally removed during the night. The results of this study suggest that even low levels of light pollution can affect the circadian rhythm thus increasing neurodegeneration [89].

Dietary habits

Nutrition is an important modifiable risk factor which plays a role in the strategy to prevent or delay the onset of dementia. Over the past years the attention has shifted from the role of single nutrients or foods to the importance of overall dietary patterns which represent a broader assessment of subject's dietary habits [90-92].

Greek Mediterranean Diet (GM Diet)

This diet is characterized by substantial intake of foods of plant origin (fruit, vegetables, breads, other forms of cereals, potatoes, beans, nuts, and seeds), the intake of fresh fruit as typical daily dessert, the use of olive oil as the principal source of fat, consumption of dairy products (principally cheese and yogurt), and fish and poultry intake in low to moderate amounts, zero to four eggs consumed weekly, low intake of red meat, and low to moderate amounts of wine, normally with meals. This diet is characterized to be low in saturated fat corresponding to ≤7–8% of total energy intake [93].

A higher adherence to the GM diet has been associated with a reduced risk of cognitive impairment, both MCI and AD, as well as the transition from MCI to AD [94, 95]. As possible mechanisms, higher adherence to GM diet has been shown to be associated with low level of C-reactive protein and lower interleukin levels. [96] Therefore a possible underlying mechanism for the neuroprotective effects of the GM diet could be due to its vascular properties and its ability to reduce inflammation, and oxidative stress, which are also associated with the pathophysiology of the degenerative disease (**Figure 7**). Another reason for the beneficial effect of GM diet could be due to the beneficial effect of the individual components, specifically vegetables, the high ratio of monounsaturated/ saturated fatty acids, and intake of alcohol and fish [95].

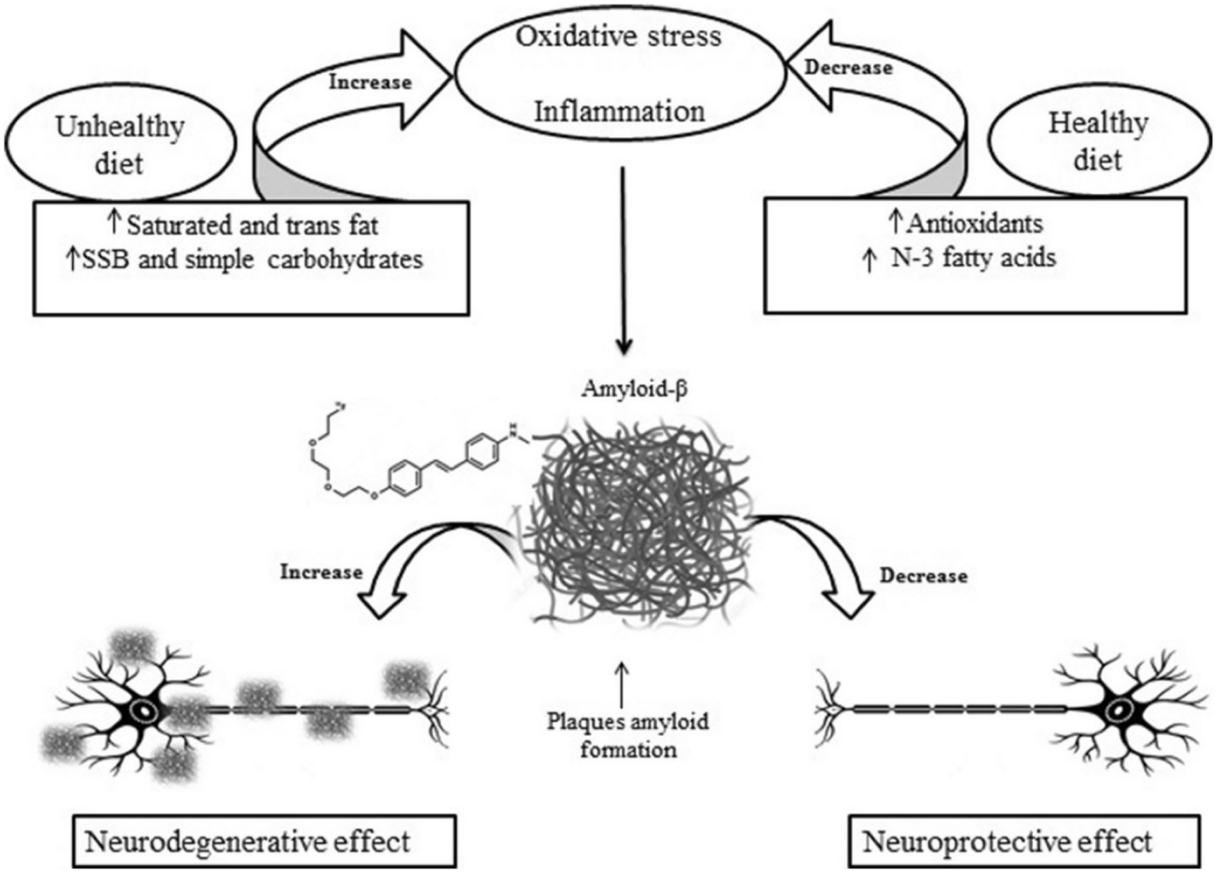


Figure 7. *Healthy and unhealthy diet in relation to AD. Adapted from [97].*

Dietary Approaches to Stop Hypertension (DASH)

DASH dietary pattern has been developed for the prevention and treatment of hypertension and it has been shown to decrease risk of both cardiovascular diseases and their risk factors, including lowering systolic and diastolic blood pressure and total cholesterol [98]. This explains why DASH diet is now recommended by the American Heart Association for the non-pharmacological management of hypertension [98]. DASH dietary pattern suggests a high consumption of plant-based foods and additionally limits the intake of saturated fats, total fat, cholesterol, and sodium. [99] In other words, this approach can increase the intake of protective nutrients such as K, Ca, Mg, fiber and vegetable proteins and, at the same time, a lower intake of refined carbohydrates and saturated fat [100].

Similarly to GM diet, it has been shown that DASH dietary pattern may prevent AD due to its effects on inflammatory pathways and oxidative stress. High intake of antioxidants, including vitamin C, vitamin E, β carotene, and flavonoids from fruits, vegetables, and vegetable oils, can enhance the antioxidant capacity and reduce inflammation (**Figure 7**) [97].

Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) dietary pattern is a healthy diet characterized by consumption of 15 components, including the increase of 10 brain

healthy food groups (namely green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, white meat (fish and poultry), olive oil instead of other oil, and wine intake limitation) as well as the decrease of 5 unhealthy food groups (namely red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). Additional general guidelines for the MIND diet are eating at least three servings of whole grains, a salad and one other vegetable, and a glass of wine each day. Moreover, nuts are considered suitable for snack on most days and beans should be consumed every other day. Poultry and berries are recommended at least twice a week and fish at least once a week. It is particularly important to limit the intake the "unhealthy food groups" as defined by the MIDN diet, especially butter (less than 1 tablespoon a day), cheese, and fried or fast food (less than a serving a week for any of the three) [101].

The possible mechanisms for the effect of this diet on AD were associated with the high intake of n-3 fatty acids from fish consumption, leading to decrease of amyloid-β formation, oxidative stress, and inflammation (**Figure 8**). In addition, these complications related to AD were improved with a high intake of flavonoids, β carotene, folate, and carotenoids from green leafy vegetables and other vegetables [97]. **Table 8** presents a comparison of the dietary components with servings for the DASH, Mediterranean and MIND dietary patterns [102].

DASH diet	Mediterranean diet	MIND pattern
Total Grains ≥7/d	Nonrefined grains >4/d	Whole grains ≥3/d
Vegetables ≥4/d	Vegetables >4/d	Green leafy ≥6/wk
	Potatoes >2/d	Other vegetables ≥1/d
Fruits ≥4/d	Fruits >3/d	Berries ≥2/wk
Dairy ≥2/d	Full-fat dairy ≤10/wk	
Meat, poultry & fish ≤ 2/d	Red meat ≤ 1/wk	Red meats and products <4/wk
	Fish >6/wk	Fish ≥1/wk
	Poultry ≤3/wk	Poultry ≥2/wk
Nuts, seeds & legumes ≥4/wk	Legumes, nuts & beans >6/wk	Beans >3/wk
		Nuts ≥5 /wk
		Fast/fried food <1/wk
Total Fat ≤ 27% of kcal		
Saturated Fat ≤ 6% of kcal		
	Olive oil ≥1/d	Olive oil primary oil
		Butter, margarine <1T/d
		Cheese<1/wk
Sweets ≤ 5/wk		Pastries, sweets <5/wk
Sodium ≤ 2400mg/d		
	Alcohol < 300mL/d but >0	Alcohol/wine 1/d

***Table 8**. Comparison of dietary components and servings for the DASH, Mediterranean and MIND diet scores. Adapted from [102].*

Treatment

The management of the patient with EOD is complex and a multidisciplinary approach is essential [4]. Many illnesses have specific treatments available, which underscores the importance of a through diagnostic evaluation.

Pharmacological treatment

The approved pharmacological treatments for young onset forms of adult neurodegenerative diseases are similar to those for LOD. Acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine may offer symptomatic benefit in AD but do not modify the disease progression. Memantine, a NMDA receptor antagonist, has also shown some symptomatic benefit in AD when used alone or in combination with acetylcholinesterase inhibitors, however, trials in FTD patients have been not demonstrated clear benefit. Depression frequently accompanies all varieties of EOD and should be targeted with antidepressants. Selective serotonin reuptake inhibitors are suggested, as they do not tend to worsen cognition. Sedatives or atypical neuroleptics may be required if a patient exhibits refractory psychotic symptoms, poses a threat to himself or others, or if other behavioral treatments have failed. However, these drugs may result in extrapyramidal syndromes and may be associated with increased mortality risk, such that they should be used at the lowest effective dosage for the shortest time possible. Regardless of the pharmacotherapy, it is important to prescribe medications according to current guidelines and ensure routine follow-up [24].

The Food and Drug Administration has recently authorized a new drug for the treatment of AD, namely aducanumab [103], which started to be used also in Italy [104]. Aducanumab is a human monoclonal antibody able to specifically bind the β-amyloid protein. A dose and time dependent reduction of Aβ plaques was observed during treatment, which appears to be related to a slowing the cognitive decline of AD patients [105].

Non-pharmacological treatment

Non-pharmacological treatment may be equally as important as pharmacological treatment in EOD. Environmental modification, including distraction with exercise or activities and restricting access to food and harmful instruments, plays an important role. Patients who wish to drive should be evaluated by an occupational therapist. Occupational and speech therapists may assist with other daily activities and alternative modes of communication. Support groups may help patients and caregivers share stories with others in similar situations. An important aspect of non-pharmacological treatment is acknowledgement of caregiver burden. EOD is particularly devastating because it strikes patients during their most productive years. Leaving the work force may accelerate a loss of autonomy and the premature loss of income and employment benefits, including health insurance and retirement, may be particularly detrimental to families dealing with EOD. Psychological and

emotional struggles such as social isolation are common as progressive disability and changes in behavior inhibit the patient and caregiver from interacting with others. Caregivers of EOD patients report a higher level of stress, burden, and depression compared to caregivers of LOD [24].

Aims

This study aims at evaluating the role of environmental factors (including occupational exposures, light at night, and dietary habits) on the risk of Alzheimer's dementia with early onset and other neurodegenerative diseases in a Northern Italy population.

Methods

Following approval by the Modena Ethics Committee (No. 186/2016), a case-control study was performed in Modena, Northern Italy.

Study populations

We recruited EOD cases among newly-diagnosed patients referred to the Cognitive Neurology Centers of Modena province, including the Modena Policlinico-University Hospital Memory Center (Modena, Italy) and the Carpi Hospital Neurology Department (Carpi, Italy) in the period October 2016-October 2019. These Centers are the only ones in province for the diagnosis of EOD. Subjects are referred from either Neurology Units, primary care services or general practitioners using critical pathways activated by the Modena Local Health Authority in order to identify and manage subjects with dementia.

Cases were recruited if they had a dementia diagnosis with symptom onset before the age of 65 and were residents in Modena province. Dementia has to be the main cause of their disability, i.e. we excluded subjects with secondary forms of dementia due pervasive developmental disorders, major psychiatric disorders, or cognitive impairment in the context of another neurological disorder in which severe disability were caused by non-cognitive symptoms (e.g. multiple sclerosis or cerebrovascular disease with severe motor disability). We recruited controls from caregivers of subjects with diagnosis of dementia of either early or late onset referring to the same Cognitive Neurology Centers.

Exposure assessment

We administrated to each subject two questionnaires: one questionnaire tailored to collect personal characteristics and factors (clinical, occupational and environmental) potentially affecting the central nervous system [106], and a detailed food frequency questionnaire (FFQ).

Lifestyle, environmental and occupational factors

In detail, the first questionnaire was subdivided into sections investigating the following sets of information: (1) personal details including date and place of birth, height and weight, marital status

and educational attainment; (2) clinical history such as date and place of EOD diagnosis (for cases only), history of any trauma requiring medical evaluation (with specific reference to head, trunk, arm and leg trauma) and any electric shock; (3) occupational history with a specific subsection aimed at assessing of exposure to toxic substances such as metals, pesticides and solvents, especially for occupational exposures in the agricultural sector; (4) nonoccupational activities potentially related to use of metals, pesticides and solvents or to traumatic events (i.e., sport); (5) other habits such as use of dietary supplements (containing or not selenium) and smoking habits (either passive or active smoking); (6) residential history, including type of source of water supply and proximity to water bodies, industries, waste disposal sites or incinerators and overhead power lines; residential use of pesticides for plants, insects and animals/pets. The questionnaire was designed to be self-administered, allowing subjects to fill it out at home and therefore in a comfortable environment. In addition, study personnel could be contacted when the subjects had doubts about items of the questionnaire. The full list of questions (in Italian) is reported in the **Appendix 1**.

Light at night (LAN) exposure

For each subject, the residential history has been collected using the first questionnaire. We geo-referenced the residential address through the use of Google Earth Pro and OpenStreetMap, using the one on the date of diagnosis for cases and on the date of recruitment for controls. In the event of a change of residence in the previous 5 years, the former address was considered.

We used two image files of annual light at night for the year 2015 (including mean and median values) for the assessment LAN exposure. These databases are pre-processed products generated by the VIIRS (Visible and Infrared Imaging Suite) sensor, mounted on the satellites of the JPSS constellation (Joint Polar-orbiting Satellite System), freely accessible on the Payne Institute website of the Colorado School of Mine in the "Earth Observation Group" section (https://eogdata.mines.edu/products/vnl/).

Characteristics of the images of these databases are: reference period as full year 2015 (as a mediation of monthly values, also averaged); format: GeoTIFF; unit of measurement: nW/cm^2/sr; spatial resolution: 15 arc seconds (pixels of about 500m at the equator).

These two databases were processed in QGIS version 3.16.6-Hannover as follows:

1. The two image files of median radiance at night have been imported as layers.
2. The dataset file of the study subjects under examination with corresponding identifying WGS84 coordinates was imported as a layer.
3. The "Sample Raster Values" function was used to extract the median radiance values at the subject residence as temporary layers.

A single dataset file was eventually implemented with the addition of the median nocturnal radiance values for the year 2015 corresponding to the LAN exposure measured in nW/cm^2/sr.

Dietary assessment

The second questionnaire is a validated semiquantitative FFQ developed within the European Prospective Investigation in Cancer project, in the version specifically validated for Northern Italy population [107, 108]. The EPIC-FFQ was designed to estimate the intake of 188 food items over the previous year in terms of frequency and amount. Photos of serving sizes were also used to assist with proper completion by participants. Full FFQ questionnaire is reported in the **Appendix 2**. Foods and beverages were categorized into major food groups and subgroups based on the common EPIC-SOFT classification, as previously reported in detail [109, 110]. The final list of food categories included the following items and subcategories: cereals and cereal products, meat and meat products, milk and dairy products, eggs, fish and seafood, vegetables, mushrooms, legumes, potatoes, fresh and dry fruits, sweet products, oils and fats, and beverages. We also computed alcohol (ethanol) intake by conversion of all quantities of alcoholic beverages into grams of ethanol per day using a previously described methodology [111].

For each study participant, we also computed scores for three a priori defined diet quality patterns: the Greek Mediterranean (GM) diet [112], the Dietary Approaches to Stop Hypertension (DASH) diet [99, 113], and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet [102, 114].

The GM diet is based on Mediterranean diet scales [112], and scoring is calculated on median level of intake of 9 items: vegetables, legumes, fruit and nuts, dairy products, cereals, meat and meat products, fish, alcohol, and the ratio of monounsaturated/ saturated fatty acids [115, 116]. The range of possible scores was 0–9, with higher scores meaning higher adherence.

The DASH diet was originally designed to reduce blood pressure [99, 113] and it has been suggested to be neuroprotective [117]. DASH diet adherence score has been calculated according to previous studies [116, 118] based on 8 components: fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains, sodium, sweetened beverages, and red and processed meats. Overall possible scores range from 8 to 40, with higher scores meaning higher adherence.

MIND diet was developed as a hybrid of Mediterranean and DASH diet which has been associated with slower cognitive decline and decreased incidence of Alzheimer's dementia as previously described [102, 114]. The MIND diet showed also beneficial effects on other neurological diseases [119-121] and a clinical trial for prevention of AD is ongoing [106]. MIND diet score is based on intake of fifteen item, namely whole grains, green leafy and other vegetables, berries, red meat, poultry, fish, legumes, nuts, fast/fried food, olive oil and other fats, cheese, sweets, and alcohol/wine. Scores ranges from 0 to 15, with higher meaning higher adherence.

Statistical analysis

In data analysis, we used adjusted multivariable unconditional logistic regression model to estimate the EOD risk and its clinical types namely early onset Alzheimer's dementia (EO-AD) and early onset frontotemporal dementia spectrum (EO-FTD). associated with environmental, occupational and lifestyle factors by computing odds ratios (ORs) and 95% confidence intervals (CIs). We included sex, age (years) and educational attainment (years of education) in the multivariable model as potential confounders and effect modifiers.

For LAN exposure, we used a multivariate unconditional logistic regression model by computing ORs and 95% CIs of EOD risk, also performing stratified analysis according type of diagnosis (i.e. EO-AD and EO-FTD). The risk of dementia was calculated according to fixed exposure categories, considering the lowest category as a reference. We also modeled the relationship between LAN and EOD risk using a cubic spline regression model with three knots (10, 50 and 90 percentiles) and using as a reference either the median or the null value. We included sex, age (years) and educational attainment (years of education) in the multivariable model as potential confounders and effect modifiers.

Similarly for analysis of role of dietary factors and dietary patterns, we performed an analysis on overall population for risk of EOD, also performing stratified analysis according type of diagnosis (i.e. EO-AD and EO-FTD). We calculated ORs and 95% CIs according to increasing tertiles based on the distribution in the control group using the lowest tertile as reference category. We also modelled the relation between dietary factors and patterns and EOD risk using restricted cubic spline model with three knots (10, 50 and 90 percentiles). We included in the multivariable model as potential confounders and effect-modifiers sex, age (years), educational attainment (years of education), and total energy intake (kcal/day).

We used 'logit', 'mkspline' and 'xblc' routines of the Stata-17.0 statistical package (Stata Corp., College Station, TX, USA, 2021) for statistical analyses.

Results

Characteristics of recruited subjects

Out of 150 eligible subjects, 144 provided a valid address and telephone in the discharge records and could be contacted. We eventually recruited 112 participants (58 EOD patients and 54 controls), with an average response rate of 78%. The main reasons for nonparticipation were lack of time to complete the questionnaires (27/32 = 84.4%) and unwillingness to contribute to the research (5/32 = 15.6%). For the analysis of dietary habits, four cases were further excluded as they did not return a reliable and complete FFQ, leaving 54 cases and 54 controls for the final analysis. Clinical diagnoses of EOD patients encompassed EO-AD (N=32 cases, 55.2%, N=30, 55.6% for diet), EO-FTD spectrum (N=19, 17 EO-FTD and 2 progressive supranuclear palsy, 32.8% and N=18, 16 EO-FTD and 2 progressive supranuclear palsy, 33.3% for diet), vascular dementia (N=5, 8.6% and N=4, 7.4% for diet), Lewy body dementia (N=1, 1.7%/1.9%) and cerebral amyloid angiopathy (N=1, 1.7%/1.9%) (**Table 9**). All controls were caregivers and family members of dementia cases, including 39 (72.2%) partners, 12 (22.2%) offspring and 3 (5.5%) siblings.

EOD diagnosis	***n* (%)**	***n* (%)**
All EOD diagnoses	58 (100)	54 (100)
Alzheimer's dementia	32 (55.2)	30 (55.6)
Frontotemporal dementia spectrum	19 (32.8)	18 (33.3)
Frontotemporal dementia	17 (29.3)	16 (29.6)
Progressive supranuclear palsy	2 (3.4)	2 (3.7)
Vascular dementia	5 (8.6)	4 (7.4)
Cerebral amyloid angiopathy	1 (1.7)	1 (1.9)
Lewy body dementia	1 (1.7)	1 (1.9)

***Table 9**. Clinical diagnosis of early onset dementia cases included in the analysis of the lifestyle, environmental and occupational factors.*

The sociodemographic characteristics of study participants, including specific features for EO-AD and EO-FTD cases, are reported in **Table 10**. The average age at questionnaire filling date was 65 years (66 for EOD cases and 64 years for referents), with a higher proportion of women (57%). The mean age of EOD onset was 59.8 years (59.7 years for EO-AD and 59.1 for EO-FTD), ranging from 45 to 65 years. Among the patients, 32.8% achieved a high school level and 5.2% reached college or more. Conversely, 38.9% of the controls obtained a high school degree, while 24.4% reached college or more. Most subjects were married (82.8% and 88.9% of cases and controls,

respectively), while widows/widowers were more common in cases compared to controls (10.3% vs. 1.8%). In addition, 38% of cases and 44% of controls reported never having smoked in their life.

Characteristics	EOD	EO-AD	EO-FTD	Controls
	n (%)	*n* (%)	*n* (%)	*n* (%)
All subjects	58 (51.8)	32 (28.6)	19 (17.0)	54 (48.2)
Age at questionnaire filling				
Mean (SD)	65.6 (5.2)	65.8 (4.5)	65.8 (5.7)	63.8 (9.6)
<65 years	22 (37.9)	12 (37.5)	6 (31.6)	28 (51.9)
≥65 years	36 (62.1)	20 (62.5)	13 (68.4)	26 (48.2)
Age at disease onset				
Mean (SD)	59.3 (4.7)	59.7 (4.1)	59.1 (5.1)	–
Sex				
Men	25 (43.1)	11 (34.4)	11 (57.9)	23 (42.6)
Women	33 (56.9)	21 (65.6)	8 (42.1)	31 (57.4)
Educational attainment				
Primary or less	16 (27.6)	8 (25.0)	5 (26.3)	11 (20.4)
Middle school	20 (34.5)	10 (31.3)	5 (42.1)	11 (20.4)
High school	19 (32.8)	12 (37.5)	5 (26.3)	21 (38.9)
College or more	3 (5.2)	2 (6.3)	1 (5.3)	11 (20.4)
Marital status				
Married/unmarried partner	48 (82.8)	25 (78.1)	17 (89.5)	48 (88.9)
Single	1 (1.7)	1 (3.1)	–	3 (5.6)
Separated/divorced	3 (5.2)	–	2 (10.5)	2 (3.7)
Widowed	6 (10.3)	6 (18.8)	–	1 (1.8)
Smoking habits				
Ever	36 (62.1)	20 (62.5)	12 (63.2)	30 (55.6)
Never	22 (37.9)	12 (37.5)	7 (36.8)	24 (44.4)

***Table 10**. Sociodemographic characteristics of early onset dementia cases (EO-AD, early onset Alzheimer's dementia; EO-FTD, early onset frontotemporal dementia) and controls.*

Substantial identical distribution was found in the subpopulation of 108 subjects with valid FFQ questionnaire after exclusion of four cases (**Table 11**).

Dementia risk according to participants' characteristics is reported in **Table 12**. Women did not show higher dementia (EOD) risk overall yet exhibited a higher EO-AD risk (OR 1.5, 95% CI 0.6–3.8) and lower EO-FTD risk (OR 0.6, 95% CI 0.2–1.7). Conversely, age seemed not to be associated with an increased risk. Concerning educational attainment, having a high school degree or more was inversely associated with EOD risk (OR 0.4, 95% CI 0.2–0.9). Living alone (single, divorced, widowed), using only those with a stable partner as referents, was associated with increased overall EOD risk (OR 1.8, 95% CI 0.6–5.6) along with an increased EO-AD risk (OR 2.4, 95% CI 0.7–8.4), whereas no change emerged for EO-FTD risk (OR 0.9, 95% CI 0.2–5.5).

Characteristics	EOD	EO-AD	EO-FTD	Controls
	n (%)	*n* (%)	*n* (%)	*n* (%)
All subjects	54 (50.0)	30 (100)	18 (100)	54 (50.0)
Age at questionnaire filling				
Mean (SD)	66.2 (4.6)	65.9 (4.5)	66.6 (4.7)	63.8 (9.6)
<65 years	19 (35.2)	11 (36.7)	5 (27.8)	28 (51.8)
≥65 years	35 (64.8)	19 (63.3)	13 (72.2)	26 (48.2)
Age at disease onset				
Mean (SD)	59.3 (4.7)	59.7 (4.1)	59.1 (5.1)	–
Sex				
Men	24 (44.4)	11 (36.7)	10 (55.6)	23 (42.6)
Women	30 (55.6)	19 (63.3)	8 (44.4)	31 (57.4)
Educational attainment				
Primary or less	13 (24.1)	6 (20.0)	5 (27.8)	11 (20.4)
Middle school	20 (37.0)	10 (33.3)	8 (44.4)	11 (20.4)
High school	18 (33.3)	12 (40.0)	4 (22.2)	21 (38.9)
College or more	3 (5.6)	2 (6.7)	1 (5.6)	11 (20.4)
Marital status				
Married/unmarried partner	45 (83.3)	23 (76.7)	16 (88.9)	48 (88.9)
Single	1 (1.9)	1 (3.3)	0 (0.0)	3 (5.6)
Separated/divorced	2 (3.7)	0 (0.0)	2 (11.1)	2 (3.7)
Widowed	6 (11.1)	6 (20.0)	0 (0.0)	1 (1.9)
Smoking habits				
Ever	34 (63.0)	18 (60.0)	12 (66.7)	30 (57.7)
Never	20 (37.0)	12 (40.0)	6 (33.3)	22 (42.3)

Table 11*. Sociodemographic characteristics of early onset dementia cases (EO-AD, early onset Alzheimer's dementia; EO-FTD, early onset frontotemporal dementia) and controls restricted to subjects with valid FFQ.*

Factor	Cases (yes/no)	Controls (yes/no)	OR	(95% CI)
Sex (women vs. men)	33/25	31/23	0.98	(0.45–2.12)
EO-AD	21/11	31/23	1.49	(0.59–3.81)
EO-FTD spectrum	8/11	31/23	0.57	(0.19–1.70)
Age (continuous)	-	-	1.03	(0.97–1.08)
EO-AD	-	-	1.03	(0.97–1.10)
EO-FTD spectrum	-	-	1.02	(0.95–1.09)
Educational attainment: High school or more vs. middle school or less	22/36	32/22	0.43	(0.20–0.94)
EO-AD	14/18	32/22	0.55	(0.22–1.35)
EO-FTD spectrum	6/13	21/22	0.35	(0.11–1.08)
Marital status: single/separated/widowed vs. married/unmarried partner	10/48	6/48	1.78	(0.56–5.59)
EO-AD	7/25	6/48	2.43	(0.70–8.42)
EO-FTD spectrum	2/17	6/48	0.91	(0.15–5.46)

Table 12. *Odds ratio (OR) with 95% confidence intervals (CI) for early onset dementia (EO-AD, early onset Alzheimer's dementia; EO-FTD, early onset frontotemporal dementia) related to sociodemographic characteristics.*

Lifestyle, environmental occupational risk factors

In **Table 13**, we report crude and adjusted risk estimates associated with occupational exposure to chemicals, stratified for EO-AD and EO-FTD clinical diagnoses. Concerning (heavy) metals, exposure to aluminum was associated with increased EOD risk, almost entirely driven by an association with EO-FTD risk (OR 4.1, 95% CI 0.5–34.5). Overall pesticide occupational exposure had an OR of 2.3, with a higher risk for all three pesticide subtypes. Moreover, in this analysis, EO-FTD cases almost entirely influenced the excess risk, since the OR in this group was 3.2 (95% CI 0.7–14.8) for overall pesticides (**Table 13**). The OR for EOD associated with overall exposure to solvents and dyes and the exposure to all subgroups was linked to increased risk, with the exception of lubricating oils. When looking at disease-specific association, exposure to these substances was linked to a much higher risk of EO-FTD (OR 2.7, 95% CI 0.7–10.4). We also found a high OR in relation to the occupational use of refrigerants, antifreezes or cooling liquids. Conversely, for both EO-AD and EO-FTD patients, a low OR emerged for exposure to electric/electronic equipment or electromagnetic fields (**Table 13**). Most of the aforementioned risk estimates were statistically very unstable due to the low number of exposed subjects.

Factor	Cases (yes/no)	Controls (yes/no)	OR	(95% CI)
Occupational exposure to toxic agents	**6/47**	**9/41**	**0.85**	**(0.22–3.29)**
EO-AD	5/26	9/41	0.60	(0.13–2.69)
EO-FTD spectrum	0/19	9/41	–	–
Lead	5/53	6/48	0.83	(0.22–3.15)
EO-AD	3/29	6/48	1.09	(0.23–5.18)
EO-FTD spectrum	1/18	6/48	0.41	(0.04–4.02)
Mercury	1/57	2/52	0.31	(0.02–4.01)
EO-AD	1/31	2/52	0.80	(0.06–10.49)
Selenium	1/57	1/53	1.56	(0.09–27.77)
EO-AD	1/31	1/53	2.62	(0.15–46.09)
Cadmium	1/57	0/54	–	–
Arsenic	0/58	0/54	–	–
Aluminum	4/54	2/52	2.59	(0.43–15.66)
EO-AD	1/31	2/52	1.01	(0.08–12.27)
EO-FTD spectrum	2/17	2/52	4.11	(0.49–34.47)
Overall pesticides	**9/49**	**5/49**	**2.28**	**(0.67–7.77)**
EO-AD	3/29	5/49	1.19	(0.25–5.58)
EO-FTD spectrum	4/15	5/49	3.19	(0.69–14.82)
Insecticides	8/50	5/49	1.98	(0.56–6.96)
EO-AD	2/30	5/49	0.78	(0.13–4.48)
EO-FTD spectrum	4/15	5/49	3.19	(0.69–14.82)
Herbicides	7/51	4/50	2.36	(0.61–9.14)
EO-AD	3/29	4/50	1.53	(0.30–7.75)
EO-FTD spectrum	2/17	4/50	2.05	(0.31–13.62)
Fungicides	2/56	2/52	1.68	(0.21–13.31)
EO-AD	1/31	2/52	1.44	(0.11–18.20)
EO-FTD spectrum	0/19	2/52	–	–

Overall solvents and dyes	**12/46**	**8/46**	**1.74**	**(0.61–5.02)**
EO-AD	5/27	8/46	1.40	(0.39–5.05)
EO-FTD spectrum	6/13	8/46	2.74	(0.72–10.38)
Oil paints	5/12	3/51	2.51	(0.62–10.15)
EO-AD	1/31	3/51	0.90	(0.08–10.04)
EO-FTD spectrum	3/16	3/51	3.34	(0.55–20.23)
Thinner	8/50	5/49	2.07	(0.58–7.46)
EO-AD	3/29	5/49	1.55	(0.31–7.68)
EO-FTD spectrum	4/15	5/49	3.06	(0.63–14.82)
Paint remover	4/54	2/52	1.77	(0.30–10.56)
EO-AD	1/31	2/52	1.02	(0.09–12.08)
EO-FTD spectrum	2/17	2/52	2.56	(0.31–21.04)
Paints	6/52	4/50	1.34	(0.34–5.37)
EO-AD	2/30	4/50	1.02	(0.17–6.33)
EO-FTD spectrum	3/16	4/50	1.88	(0.35–10.10)
Adhesives	2/56	1/53	2.68	(0.22–32.63)
EO-AD	2/30	1/53	5.24	(0.44–63.05)
Print inks and dyes	4/54	3/51	1.74	(0.35–8.72)
EO-AD	3/29	3/51	2.39	(0.41–13.79)
EO-FTD spectrum	1/18	3/51	1.47	(0.12–17.90)
Lubricating oils	3/55	4/50	0.80	(0.16–3.94)
EO-FTD spectrum	3/16	4/50	2.55	(0.47–13.94)
Refrigerants, antifreezes, cooling liquids	1/57	1/53	1.73	(0.10–29.84)
EO-AD	1/31	1/53	3.01	(0.17–54.25)
Degreasing agents	3/55	1/53	2.38	(0.23–24.40)
EO-AD	3/29	1/53	5.52	(0.51–59.14)
Solvents (e.g., toluene, xylene)	2/56	2/52	1.04	(0.13–8.22)
EO-AD	1/31	2/52	1.13	(0.09–13.60)
EO-FTD spectrum	1/18	2/52	1.46	(0.11–19.43)
Dry clean products	3/55	0/54	–	–
Anesthetic gas	1/57	0/54	–	–
Electric and electronic equipment	4/54	9/45	0.54	(0.14–2.00)
EO-AD	3/29	9/45	0.78	(0.18–3.42)
EO-FTD spectrum	1/18	9/45	0.37	(0.04–3.53)
Electromagnetic fields	1/57	3/51	0.37	(0.04–3.81)
EO-AD	1/31	3/51	0.71	(0.07–7.32)
Exposure during agricultural occupation				
Fertilizers	4/54	3/51	1.96	(0.39–9.74)
EO-AD	1/31	3/51	0.70	(0.07–7.36)
EO-FTD spectrum	2/17	3/51	3.02	(0.40–23.02)
Pesticides	7/51	3/51	3.11	(0.72–13.32)
EO-AD	3/29	3/51	2.07	(0.38–11.41)
EO-FTD spectrum	3/16	3/51	4.73	(0.76–29.23)
Disinfectants	2/56	1/53	2.65	(0.2–34.84)
EO-AD	0/32	1/53	–	–
EO-FTD spectrum	2/17	1/53	9.56	(0.68–135.1)
Detergents	2/56	1/53	2.26	(0.17–30.78)
EO-FTD spectrum	2/17	1/53	8.69	(0.58–130.87)
Solvents	2/56	0/54	–	–
Oils	4/54	3/51	1.71	(0.34–8.48)
EO-AD	2/30	3/51	1.27	(0.19–8.42)
EO-FTD spectrum	2/17	3/51	3.02	(0.40–23.02)
Diesel/gasoline	4/54	4/50	1.14	(0.26–5.06)

EO-AD	1/31	4/50	0.47	(0.05–4.58)
EO-FTD spectrum	2/17	4/50	1.74	(0.26–11.49)
Work accident with toxicant exposure	0/58	1/53	–	–
Nausea/indisposition due to occupational exposure	1/57	1/53	0.98	(0.06–16.23)

Table 13. *Odds ratio (OR) with 95% confidence intervals (CI) for early onset dementia (EO-AD, early onset Alzheimer's dementia; EO-FTD, early onset frontotemporal dementia) related to occupational exposure to toxic agents.*

Restricting the assessment to agricultural exposure, the OR for EOD associated with pesticides further increased. A high OR for EOD was also generally found for other groups of chemicals such as fertilizers (OR 2.0, 95% CI 0.4–9.7), disinfectants (OR 2.7, 95% CI 0.2–34.8), detergents (OR 2.3, 95% CI 0.2–30.8) and oils (OR 1.7, 95% CI 0.3–8.5). All of these kinds of exposures were linked to a higher risk of EO-FTD (**Table 13**).

As shown in **Table 14**, history of any trauma requiring medical evaluation before disease onset was not associated with EOD risk. Nonetheless, we found a higher value in the analysis limited to head trauma (OR 1.5, 95% CI 0.3–4.1), particularly limiting analyses to EO-FTD cases (OR 3.4, 95% CI 0.8–14.6). Exposure to upper arm trauma showed an increased risk, in this case affected by EO-AD cases (OR 2.2, 95% CI 0.7–6.9). Playing sports was inversely associated with disease risk (OR 0.4, 95% CI 0.2–0.9), with an equal impact for both EO-FTD and EO-AD patients (OR 0.3, 95% CI 0.1–1.3 and 0.4, 95% CI 0.1–1.0 respectively). This was confirmed when we limited the analysis to competitive sports only. Conversely, a higher OR emerged for two professional sports, namely football (OR 2.2, 95% CI 0.5–9.3) and cycling (OR 2.3, 95% CI 0.4–13.4). When looking at type-specific association, both sports were linked to a higher risk of EO-FTD (OR 2.6, 95% CI 0.4–15.9 for football and OR 4.4, 95% CI 0.6–30.9 for cycling) compared with EO-AD (OR 1.8, 95% CI 0.3–10.1 and 0.6, 95% CI 0.1–7.6 respectively). Concerning other leisure activities and habits, we found no increased risk in association with hunting, fishing and model-making. Gardening and overall pesticide use during gardening were not associated with EOD risk, while the use of fungicides during gardening was linked to a slightly increased risk, due to a markedly increased risk in EO-AD patients (**Table 14**).

Factor	**Cases (yes/no)**	**Controls (y/n)**	**OR**	**(95% CI)**
Trauma that need medical evaluation	**23/32**	**22/31**	**0.93**	**(0.42–2.07)**
EO-AD	13/18	22/31	0.99	(0.39–2.50)
EO-FTD spectrum	8/9	22/31	1.17	(0.37–3.70)
Head trauma	9/46	6/47	1.54	(0.47–4.99)
EO-AD	3/28	6/47	0.98	(0.21–4.51)
EO-FTD spectrum	5/12	6/47	3.43	(0.80–14.60)
Trunk trauma	0/55	2/51	–	–

EO-AD	0/31	2/51	–	–
EO-FTD spectrum	0/17	2/51	–	–
Upper arm trauma	10/45	8/45	1.38	(0.47–4.03)
EO-AD	8/23	8/45	2.16	(0.68–6.93)
EO-FTD spectrum	2/15	8/45	0.83	(0.13–5.15)
Lower arm trauma	13/42	13/40	0.85	(0.34–2.13)
EO-AD	9/22	13/40	1.13	(0.40–3.19)
EO-FTD spectrum	3/14	13/40	0.51	(0.12–2.20)
Electric shock/trauma	1/57	2/52	0.18	(0.01–2.22)
EO-AD	0/32	2/52	–	–
EO-FTD spectrum	0/19	2/52	–	–
Leisure activities				
Hunting	2/56	2/52	1.03	(0.13–8.25)
EO-FTD spectrum	2/17	2/52	2.92	(0.33–25.90)
Fishing	6/52	7/47	0.65	(0.18–2.35)
EO-AD	1/31	7/47	0.19	(0.02–1.82)
EO-FTD spectrum	4/15	7/47	1.20	(0.25–5.65)
Painting	7/47	6/46	1.08	(0.32–3.66)
EO-AD	4/26	6/46	1.28	(0.30–5.49)
EO-FTD spectrum	3/14	6/46	1.60	(0.31–8.15)
Model-making	3/55	3/51	1.11	(0.19–6.42)
EO-AD	1/31	3/51	0.71	(0.06–8.02)
EO-FTD spectrum	2/17	3/51	2.21	(0.28–17.20)
Gardening	22/36	26/28	0.71	(0.32–1.57)
EO-AD	13/19	26/28	0.87	(0.34–2.24)
EO-FTD spectrum	6/13	26/28	0.48	(0.15–1.55)
Using pesticides during gardening	7/51	8/46	0.84	(0.27–2.55)
EO-AD	4/28	8/46	0.84	(0.23–3.11)
EO-FTD spectrum	2/17	8/46	0.63	(0.11–3.49)
Using herbicides during gardening	4/54	4/50	1.31	(0.28–6.08)
EO-AD	2/30	4/50	1.10	(0.17–7.07)
EO-FTD spectrum	1/18	4/50	1.13	(0.10–13.45)
Using fungicides during gardening	6/52	4/50	1.56	(0.40–6.10)
EO-AD	5/27	4/50	2.95	(0.67–13.0)
EO-FTD spectrum	1/18	4/50	0.58	(0.06–6.12)
Developing pictures in darkroom	1/57	1/53	1.00	(0.06–17.79)
EO-AD	1/31	1/53	2.21	(0.12–14.15)
Playing sport	**15/43**	**28/26**	**0.36**	**(0.15–0.89)**
EO-AD	8/24	28/26	0.37	(0.13–1.04)
EO-FTD spectrum	5/14	28/26	0.34	(0.09–1.26)
Playing competitive sport	4/54	8/46	0.45	(0.11–1.74)
EO-AD	1/31	8/46	0.19	(0.02–1.75)
EO-FTD spectrum	3/16	8/46	1.05	(0.21–5.15)
Football	7/51	4/50	2.23	(0.54–9.26)
EO-AD	3/29	4/50	1.78	(0.32–10.06)
EO-FTD spectrum	3/16	4/50	2.62	(0.43–15.90)
Volleyball	2/56	6/48	0.36	(0.07–1.92)
EO-AD	1/31	6/48	0.31	(0.03–2.80)
EO-FTD spectrum	1/18	6/48	0.66	(0.07–6.20)
Cycling	5/53	2/52	2.28	(0.39–13.43)
EO-AD	1/31	2/52	0.60	(0.05–7.56)
EO-FTD spectrum	3/16	2/52	4.37	(0.62–30.93)
Swimming	2/56	12/42	0.17	(0.03–0.84)

EO-AD	2/30	12/42	0.28	(0.06–1.45)
Athletics	2/56	6/48	0.29	(0.05–1.56)
EO-AD	1/31	6/48	0.24	(0.03–2.13)
EO-FTD spectrum	1/18	6/48	0.49	(0.05–4.74)
Running/trekking	1/57	4/50	0.34	(0.03–3.25)
EO-FTD spectrum	1/18	4/50	1.13	(0.11–12.09)
Use of dietary supplements containing selenium in the past 20 years	14/44	8/46	2.50	(0.89–7.02)
EO-AD	6/26	8/46	2.01	(0.57–7.10)
EO-FTD spectrum	7/12	8/46	7.40	(1.65–33.19)
Excluding specific neuroprotective supplements after onset of disease	11/47	8/46	1.73	(0.60–4.99)
EO-AD	3/29	8/46	0.78	(0.18–3.41)
EO-FTD spectrum	8/11	8/46	8.73	(2.01–38.00)
Use of selenized potatoes	7/51	11/43	0.55	(0.19–1.62)
EO-AD	3/29	11/43	0.40	(0.10–1.63)
EO-FTD spectrum	3/16	11/43	0.70	(0.16–3.05)
Ever smoking	35/23	30/24	1.28	(0.58–2.86)
EO-AD	19/13	30/24	1.35	(0.51–3.55)
EO-FTD spectrum	12/7	30/24	1.31	(0.42–4.09)
Current smoking	10/48	10/44	1.01	(0.37–2.79)
EO-AD	5/27	10/44	0.87	(0.25–2.99)
EO-FTD spectrum	3/16	10/44	1.09	(0.24–4.89)
Passive smoking exposure	15/43	12/42	1.17	(0.47–2.88)
EO-AD	9/23	12/42	1.24	(0.44–3.46)
EO-FTD spectrum	5/14	12/42	1.22	(0.33–4.50)

***Table 14**. Odds ratio (OR) with 95% confidence intervals (CI) for early onset dementia (EO-AD, early onset Alzheimer's dementia; EO-FTD, early onset frontotemporal dementia) according to trauma and leisure activities.*

Intake of selenium-containing dietary supplements in the 20 years before recruitment yielded an OR of 2.5 (95% CI 0.9–7.0). This increased risk persisted even after excluding the use of neuroprotective supplements after disease onset (OR 1.7, 95% CI 0.6–5.0), reaching an OR of 8.7 (95% CI 2.0–38.0) in stratified analyses for EO-FTD cases. Finally, history of smoking was associated with slightly increased risk (OR 1.3, 95% CI 0.6–2.9). A similarly marginal increased risk emerged for secondhand smoke exposure (OR 1.2, 95% CI 0.5–2.9), with no difference between the two stratified groups.

ORs for residential history are reported in **Table 15**. Ever having lived less than 3 km from waste disposal sites was associated with an increased risk (OR 1.1, 95% CI 0.5–2.5), as was the case for having lived in the countryside or having had a farm (OR 1.8, 95% CI 0.8–4.0), along with the use of private sources (wells or fountains) of drinking water (OR 2.0, 95% CI 0.8–5.2). Finally, residential use of pesticides was associated with a generally increased risk when used for outdoor plants (OR 1.3, 95% CI 0.4–4.1), rodents and rats (OR 1.8, 95% CI 0.3–12.3) or bugs (OR 1.3, 95%

CI 0.5–3.2), particularly ground bugs (OR 1.9, 95% CI 0.6–6.4) but not flying bugs (1.0, 95% CI 0.4–2.4).

Factors	Cases (y/n)	Controls (y/n)	OR	(95% CI)
Residential history				
Ever lived in the countryside or had a farm	27/31	21/33	1.79	(0.80–4.03)
EO-AD	15/17	21/33	1.54	(0.61–3.90)
EO-FTD spectrum	8/11	21/33	1.68	(0.52–5.41)
Ever used private well or a fountain for drinking water	16/42	11/43	2.04	(0.80–5.21)
EO-AD	9/23	11/43	2.14	(0.71–6.47)
EO-FTD spectrum	5/14	11/43	1.86	(0.50–6.93)
Ever used private well or fountain for irrigation	5/53	10/44	0.46	(0.14–1.48)
EO-AD	1/31	10/44	0.17	(0.02–1.41)
EO-FTD spectrum	2/17	10/44	0.54	(0.10–2.89)
Ever lived less than 3 km from water bodies	25/33	24/30	1.14	(0.52–2.52)
EO-AD	14/18	24/30	1.11	(0.44–2.81)
EO-FTD spectrum	6/13	24/30	0.69	(0.22–2.17)
Having lived near:				
Waste incinerator	1/57	3/51	0.28	(0.03–2.99)
EO-AD	1/31	3/51	0.49	(0.05–5.13)
Waste disposal site	4/54	3/51	1.88	(0.38–9.40)
EO-AD	3/29	3/51	2.54	(0.45–14.52)
EO-FTD spectrum	1/18	3/51	1.46	(0.12–17.19)
Toxic plant/industry	11/47	14/40	0.63	(0.25–1.61)
EO-AD	5/27	14/40	0.51	(0.16–1.62)
EO-FTD spectrum	4/15	14/40	0.68	(0.18–2.55)
Overhead power lines	7/51	11/43	0.67	(0.23–1.99)
EO-AD	2/30	11/43	0.28	(0.06–1.39)
EO-FTD spectrum	3/16	11/43	1.04	(0.23–4.58)
Residential use of pesticides	**16/42**	**18/36**	**1.00**	**(0.42–2.35)**
EO-AD	7/25	18/36	0.68	(0.24–1.98)
EO-FTD spectrum	5/14	18/36	0.87	(0.26–2.94)
By substrate:				
Plants	7/51	8/46	0.92	(0.30–2.84)
EO-AD	2/30	8/46	0.40	(0.08–2.06)
EO-FTD spectrum	3/16	8/46	1.50	(0.33–6.90)
Outdoor plants	7/51	6/48	1.25	(0.38–4.10)
EO-AD	2/30	6/48	0.56	(0.10–3.02)
EO-FTD spectrum	3/16	4/48	1.97	(0.41–9.45)
Indoor plants	2/56	4/50	0.58	(0.10–3.56)
EO-AD	1/31	4/50	0.45	(0.04–4.53)
EO-FTD spectrum	1/18	4/50	1.08	(0.10–11.62)
Bugs	15/43	14/40	1.29	(0.53–3.16)
EO-AD	8/24	14/40	1.26	(0.43–3.70)
EO-FTD spectrum	4/15	14/40	0.86	(0.23–3.25)
Flying bugs	12/46	14/40	0.97	(0.38–2.44)
EO-AD	6/26	14/40	0.85	(0.27–2.64)
EO-FTD spectrum	3/16	14/40	0.66	(0.16–2.76)
Ground bugs	8/50	6/48	1.89	(0.56–6.40)

EO-AD	5/27	6/48	2.13	(0.54–8.47)
EO-FTD spectrum	2/17	6/48	1.24	(0.20–7.67)
Rodents and rats	3/55	2/52	1.83	(0.27–12.26)
EO-AD	2/30	2/52	1.99	(0.24–16.28)
EO-FTD spectrum	1/18	2/52	2.24	(0.16–31.13)
Pets	8/50	11/43	0.77	(0.27–2.17)
EO-AD	3/29	11/43	0.44	(0.11–1.81)
EO-FTD spectrum	4/15	11/43	1.23	(0.32–4.76)
Municipal pesticides use	22/36	21/33	1.05	(0.47–2.33)
EO-AD	13/19	21/33	1.22	(0.48–3.09)
EO-FTD spectrum	7/12	21/33	0.91	(0.30–2.80)

Table 15. *Odds ratio (OR) with 95% confidence interval (CI) for early onset dementia (EO-AD, early onset Alzheimer's dementia; EO-FTD, early onset frontotemporal dementia) related to residential history.*

Light at night

Figure 8 shows the satellite maps of the light at night exposure of the Emilia-Romagna region and of the municipality of Modena used for the assessment of LAN exposure of the subjects recruited in the study. Controls are exposed to an average LAN level of 25.3 nW/cm^2/sr (standard deviation-SD: 16.8) with a median value of 25.8 nW/cm^2/sr (interquartile range-IQR: 7.0–38.1). EOD cases show similar values of LAN levels with mean of 25.2 nW/cm^2/sr (SD: 15.6) and median of 25.8 nW/cm^2/sr (IQR: 9.7–38.1). Conversely EO-AD cases demonstrate higher mean and median values of 28.4 nW/cm^2/sr (SD: 15.9) and 29.9 nW/cm^2/sr (IQR: 13.3–40.3), respectively, compared to EO-FTD cases with mean and median values of 24.4 nW/cm^2/sr (SD: 14.6) and 27.1 nW/cm^2/sr (IQR: 15.0–37.5), respectively.

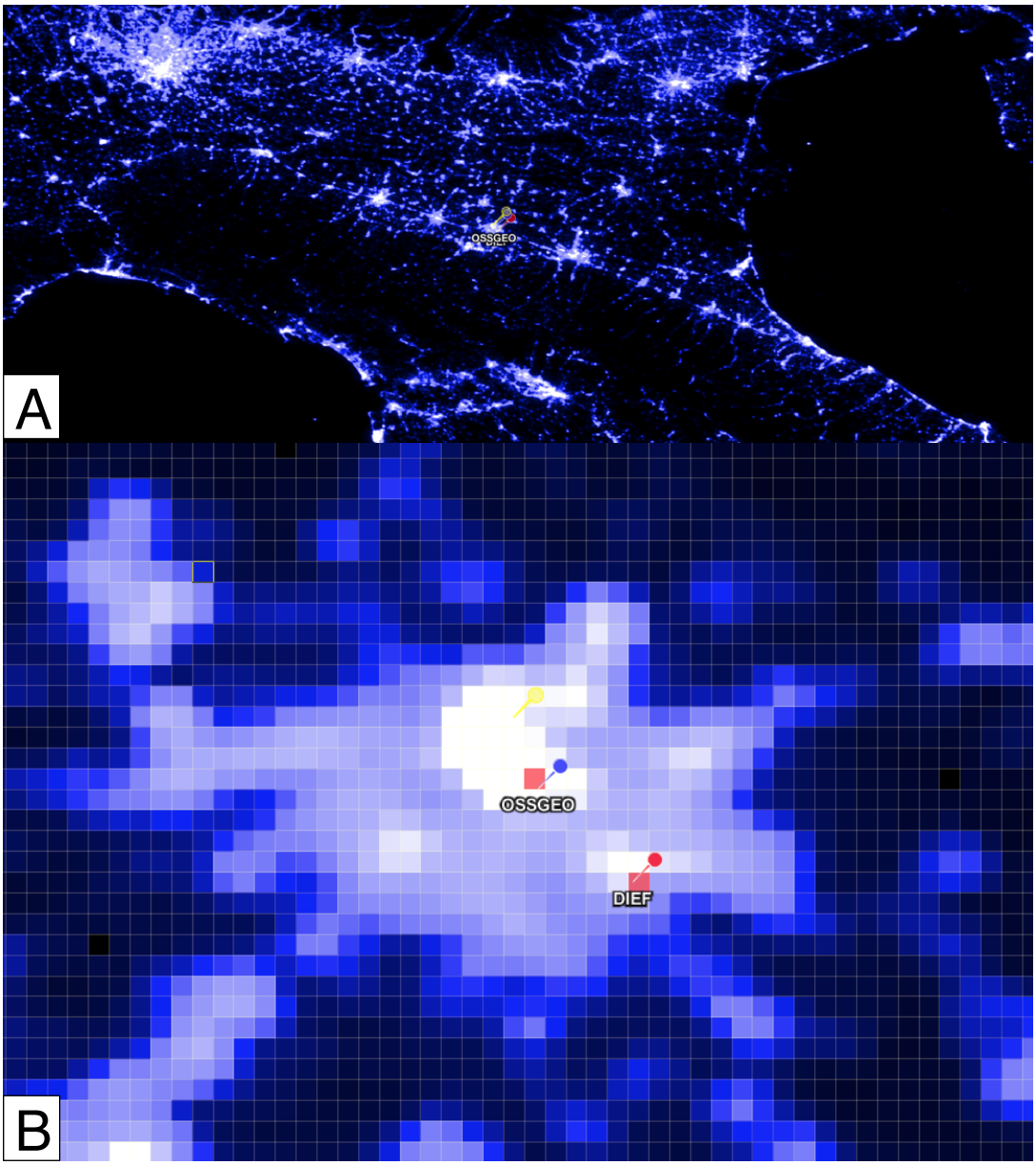


Figure 8. *Light at night exposure map of the Emilia-Romagna region (A) and of the municipality of Modena (B) obtained using satellites of the JPSS constellation in 2015. The OSSGEO and DIEF points indicate the meteorological stations of the University of Modena and Reggio Emilia, namely the Geophysical Observatory of Modena in the city center and the Department Engineering "Enzo Ferrari" Engineering Department, respectively. The pixel measurement is 500 m x 500 m.*

Increased LAN exposure (**Table 16**) shows an increased though imprecise EOD risk for the intermediate exposure category with an OR of 1.36 (95% CI 0.54–3.39) not confirmed in the highest exposure category with an OR of 1.04 (95% CI 0.32–3.34). As regards spline analysis, there is no evidence of an increase in risk of EOD with increasing LAN exposure either using median or null value as reference (**Figure 9**).

LAN (nW/cm²/sr)	50th	EOD		
		Cases/ Controls	OR	(95% CI)
Continuous (1-unit) increase			1.02	(0.98–1.03)
LAN median value				
Below median value (ref.)	6.7	28/26	1.00	–
Above median value	37.8	30/28	1.10	(0.50–2.40)
LAN tertiles				
1st tertile (ref.)	5.2	19/18	1.00	–
2nd tertile	25.1	21/18	1.25	(0.49–3.20)
3rd tertile	42.1	18/18	1.10	(0.42–2.90)
LAN fixed categories				
<10 (ref.)	4.6	15/15	1.00	–
≥10 and < 40	26.8	32/27	1.36	(0.54–3.39)
≥ 40	47.1	11/12	1.04	(0.32–3.34)

***Table 16**. Odds ratio (OR) with 95% confidence interval (CI) for early onset dementia (EOD) related to light at night (LAN) exposure.*

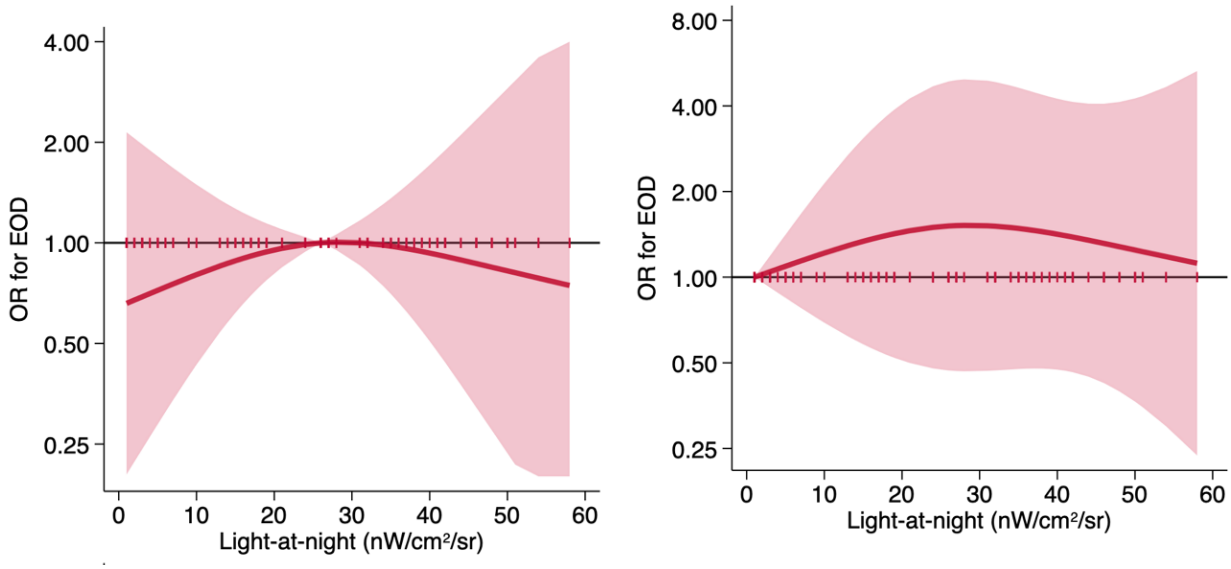


***Figure 9.** Spline regression analysis of EOD risk for increasing light at night exposure using median (25.8 nW/cm²/sr) or null value as reference.*

Among the 32 subjects with EO-AD diagnosis, increased LAN exposure show an increase risk for the intermediate and high exposure with OR of 1.60 (95% CI 0.51–4.99) and 1.89 (95% CI 0.47–7.54) (**Table 17**). In the spline analysis, a substantial linear increase can be noted for increasing LAN exposure, though the high imprecision of all estimates **Figure 10**.

LAN (nW/cm²/sr)	50th	EO-AD			EO-FTD		
		Cases/ Controls	OR	(95% CI)	Cases/ Controls	OR	(95% CI)
Continuous (1-unit) increase			1.02	(0.99–1.05)		1.08	(1.00–1.19)
LAN median value							
Below median value (ref.)	6.7	14/26	1.00	–	9/26	1.00	–
Above median value	37.8	18/28	1.30	(0.52-3.29)	10/28	5.87	(0.59–58.14)
LAN tertiles							
1st tertile (ref.)	5.2	9/18	1.00	–	6/18	1.00	–
2nd tertile	25.1	11/18	1.43	(0.46–4.52)	7/18	2.47	(0.06–99.70)
3rd tertile	42.1	12/18	1.69	(0.52–5.43)	6/18	22.26	(0.59–841.51)
LAN fixed categories							
<10 (ref.)	4.6	7/15	1.00	–	4/15	1.00	–
≥10 and < 40	26.8	17/27	1.60	(0.51–4.99)	12/27	3.70	(0.11–125.07)
≥ 40	47.1	8/12	1.89	(0.47–7.54)	3/12	16.61	(0.42–650.57)

Table 17*. Odds ratio (OR) with 95% confidence interval (CI) for early onset dementia (EO-AD, early onset Alzheimer's dementia; EO-FTD, early onset frontotemporal dementia) related to light at night (LAN) exposure.*

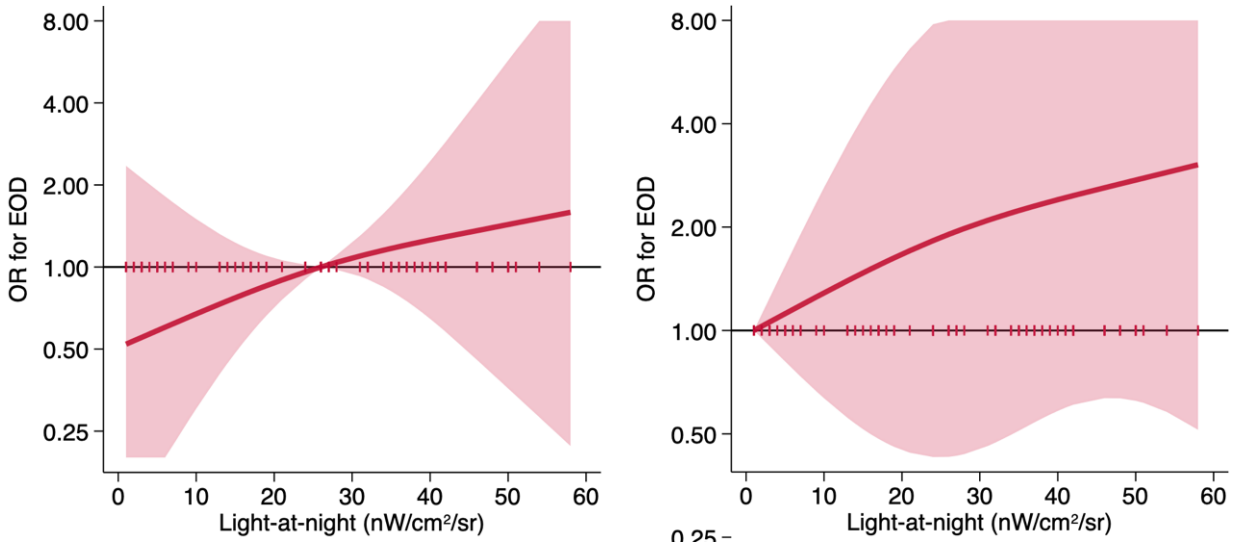


Figure 10. *Spline regression analysis of EO-AD risk for increasing light at night exposure using median (25.8 nW/cm²/sr) or null value as reference.*

As regards the 19 EO-FTD cases, we found that LAN exposure is associated with increase in risk in the intermediate exposure (OR: 1.58, 95% CI 0.41–6.10), but not in the highest category (OR: 0.77, 95% CI 0.13–4.69) (**Table 17**). Similarly in the spline analysis, we did not find a clear indication of a positive relation with LAN exposure (**Figure 11**).

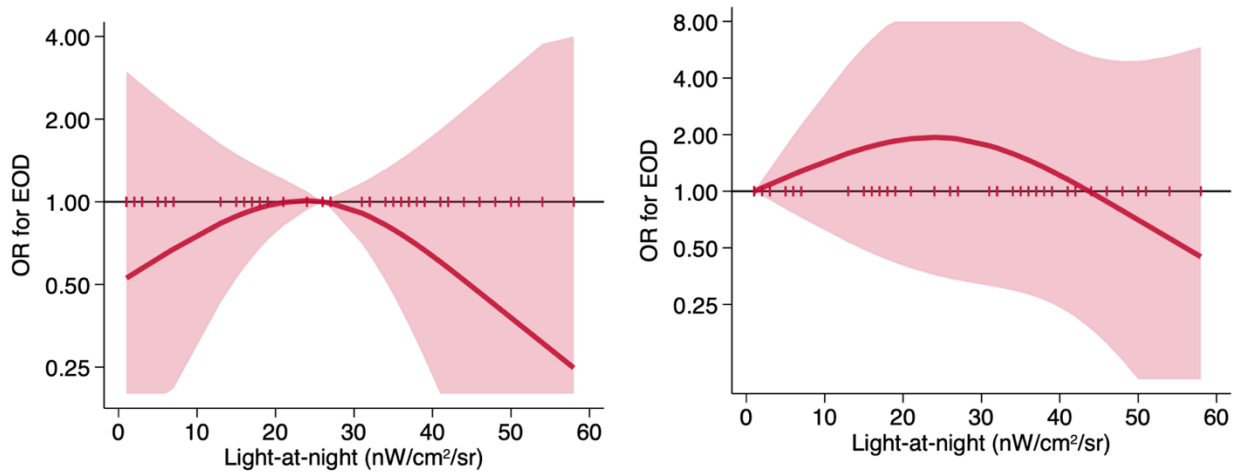


Figure 11. *Spline regression analysis of EO-FTD risk for increasing light at night exposure using median (25.8 nW/cm²/sr) or null value as reference.*

Dietary habits

Table 18 and **Table 19** show the average intake of food and beverages for the study participants. No subjects reported a special dietary regimen for medical purposes. Total energy intake was slightly higher in cases compared to controls. As regards cereal products, cases were shown to have a higher intake compared to controls, in particular EO-FTD subjects. Cases had a slightly higher intake of meat products compared with controls, including red and white meat, and a higher intake of dairy products, particularly milk and yogurt, especially in EO-AD compared to EO-FTD cases. Cases also showed a substantially similar intake of fish and seafood, but a higher consumption of preserved and tinned fish particularly for EO-FTD cases, a lower intake of piscivorous fish and crustaceans/mollusks, especially in EO-FTD cases. Cases also showed a lower intake of overall vegetables, with similar results for all vegetable types but cabbage, a lower intake of potatoes and legumes. Overall, fresh fruit intake was somewhat higher in cases than controls, although the former showed a lower intake of citrus fruits yet a higher intake of all other fruits, with similar results across EO-AD and EO-FTD. Dry fruit intake was lower in cases than in controls, particularly for nuts and seeds and especially in EO-FTD, characterized by a much lower intake of both overall dry fruit and nuts and seeds. Sweet intake was higher in cases, particularly due to a higher consumption of ice-cream, biscuits and dry cakes, while consumption of chocolate-based products was lower. Cases consumed less oils and fats, with a lower intake of both vegetable oils and olive oil. Concerning beverages, cases had a lower intake of coffee and tea, but results were the opposite in the subgroup analysis according to EOD diagnosis, with higher intake in EO-AD cases and a much lower one in EO-FTD cases, who showed very low tea consumption. Wine consumption was substantially similar in cases and controls, with EO-AD cases reporting a lower

intake and EO-FTD a higher one, mainly due to the higher consumption of white wine. A higher intake of aperitif wines and beers was reported for controls. Overall alcohol intake was comparable in cases and controls, although EO-FTD cases showed a much higher intake compared to EO-AD cases. Concerning non-alcoholic beverages, cases reported a higher intake of fruit juices and a lower consumption of soft drinks.

	Controls		EOD Cases	
	Mean (SD)	N (%)	Mean (SD)	N (%)
Total energy intake (Kcal/day)	1867.8 (803.9)	–	2010.4 (707.0)	–
Food (g/day)		54 (100)		54 (100)
Cereals and cereal products	168.9 (82.7)	0 (0.0)	185.1 (116.5)	1 (1.85)
Pasta and other grains	42.0 (35.0)	1 (1.85)	56.4 (37.3)	1 (1.85)
Rice	4.2 (4.2)	11 (20.37)	6.7 (8.5)	11 (20.37)
Bread	72.4 (59.4)	2 (3.70)	83.2 (81.1)	8 (14.81)
Pizza, crackers, and other salty snacks	50.3 (38.1)	1 (1.85)	38.8 (32.4)	2 (3.70)
Meats and meat products	96.9 (54.6)	1 (1.85)	106.1 (59.8)	0 (0.0)
Red meat	51.3 (40.0)	2 (3.70)	54.2 (45.0)	2 (3.70)
White meat	21.8 (18.8)	3 (5.56)	27.8 (23.9)	1 (1.85)
Processed meat	22.2 (18.2)	1 (1.85)	23.1 (19.4)	0 (0.0)
Offal	1.7 (5.9)	40 (74.07)	1.1 (3.2)	41 (75.93)
Milk and dairy products	182.5 (139.8)	0 (0.0)	276.1 (300.4)	0 (0.0)
Milk and yogurt	152.2 (133.5)	12 (22.22)	238.1 (299.2)	10 (18.52)
Milk	108.9 (112.8)	17 (31.48)	179.3 (291.6)	17 (31.48)
Yogurt	43.3 (72.5)	27 (50.00)	58.8 (92.0)	24 (44.44)
Cheese	30.3 (23.6)	(0.0)	38.0 (32.8)	0 (0.0)
Fresh cheese	12.4 (13.5)	8 (14.81)	13.7 (14.2)	12 (22.22)
Aged cheese	17.1 (14.9)	3 (5.56)	22.4 (23.3)	2 (3.70)
Eggs	13.2 (13.1)	4 (7.41)	14.8 (11.6)	3 (5.56)
Fish and seafood	30.9 (23.6)	4 (7.41)	30.0 (24.1)	4 (7.41)
Fish	24.8 (19.0)	5 (9.26)	24.9 (21.2)	5 (9.26)
Preserved and tinned fish	8.7 (7.7)	8 (14.81)	12.1 (14.6)	7 (12.96)
Non-piscivorous fish	8.3 (13.5)	14 (25.93)	7.9 (10.9)	14 (25.93)
Piscivorous fish	7.9 (11.0)	17 (31.48)	4.9 (7.2)	21 (38.89)
Crustaceans and molluscs	6.0 (9.2)	8 (22.22)	5.1 (7.0)	14 (25.93)
All vegetables	143.0 (91.8)	0 (0.0)	113.5 (78.5)	0 (0.0)
Leafy vegetables	26.7 (22.1)	0 (0.0)	20.2 (16.6)	0 (0.0)
Tomatoes	47.2 (52.6)	0 (0.0)	41.3 (42.7)	1 (1.85)
Root vegetables	34.5 (34.1)	7 (12.96)	24.3 (27.1)	13 (24.07)
Cabbage	4.9 (7.7)	20 (37.04)	5.1 (8.4)	16 (29.63)
Other vegetables	29.6 (21.3)	0 (0.0)	22.6 (20.1)	3 (5.56)
Mushrooms	2.5 (2.6)	11 (20.37)	2.2 (2.8)	21 (38.89)
Legumes	21.1 (21.5)	0 (0.0)	19.6 (17.3)	4 (7.41)
Potatoes	22.5 (29.6)	0 (0.0)	15.7 (14.7)	3 (5.56)
Fresh fruit	248.3 (137.9)	0 (0.0)	259.0 (155.4)	0 (0.0)
Citrus fruit	58.5 (50.4)	2 (3.70)	45.4 (39.5)	5 (9.26)
All other fruit	189.8 (101.3)	0 (0.0)	213.7 (133.1)	2 (3.70)
Dry fruits, nuts and seeds	3.9 (5.1)	4 (7.41)	2.3 (4.1)	8 (14.81)
Dry fruits	0.6 (1.2)	20 (37.04)	0.4 (1.2)	29 (53.70)
Nuts and seeds	3.3 (4.7)	5 (9.26)	1.9 (3.4)	8 (14.81)
Sweets, chocolate, cakes, etc.	113.9 (130.4)	1 (1.85)	128.8 (84.3)	1 (1.85)
Sugar, non-chocolate confectionery	26.7 (39.4)	11 (20.37)	27.5 (39.1)	10 (18.52)
Chocolate, candy bars, etc.	7.7 (15.4)	22 (40.74)	4.1 (5.8)	19 (35.19)
Ice-cream	15.8 (22.8)	10 (18.52)	22.8 (27.4)	8 (14.81)
Cakes, pies and pastries	52.0 (101.3)	6 (11.11)	55.6 (49.7)	7 (12.96)

Biscuits, dry cakes	11.7 (15.1)	16 (29.63)	18.9 (23.2)	13 (24.07)
Oils and fats	25.0 (13.3)	0 (0.0)	21.4 (11.6)	0 (0.0)
Vegetable fats and non-olive oils	3.0 (4.2)	16 (29.63)	1.9 (2.4)	18 (33.33)
Olive oil	19.6 (12.8)	1 (1.85)	17.4 (10.7)	2 (3.70)
Butter and other animal fats	2.4 (4.5)	6 (11.11)	2.1 (3.1)	11 (20.37)
Beverages				
Coffee and tea	137.8 (163.6)	2 (3.70)	112.9 (152.4)	10 (18.52)
Coffee	69.9 (44.2)	7 (12.96)	67.0 (71.0)	15 (27.78)
Tea	67.9 (156.8)	28 (51.85)	45.9 (136.7)	38 (70.37)
Wine	86.7 (159.0)	24 (44.44)	84.5 (139.0)	29 (53.70)
Red wine	28.5 (64.7)	29 (53.70)	42.8 (89.4)	34 (62.96)
White wine	58.2 (130.9)	29 (53.70)	41.7 (101.4)	34 (62.96)
Aperitif wines and beers	44.9 (133.6)	25 (46.30)	17.1 (63.6)	37 (68.52)
Spirits and liqueurs	1.2 (4.2)	36 (66.67)	0.1 (0.4)	48 (88.89)
Fruit juices	68.8 (140.1)	30 (55.56)	113.3 (201.8)	19 (35.19)
Soft drinks	73.8 (184.8)	37 (68.52)	42.1 (94.5)	35 (64.81)
Alcohol intake	10.3 (15.7)	6 (11.11)	10.1 (19.5)	9 (18.67)

Table 18. *Food and beverages mean (standard deviation - SD) intake and number (%) of consumers in the study population. Early onset dementia (EOD).*

	EO-AD		**EO-FTD**	
	Mean (SD)	**N (%)**	**Mean (SD)**	**N (%)**
Total energy intake (Kcal/day)	1973.2 (769.1)		2106.0 (680.7)	
Food (g/day)		30 (100)		18 (100)
Cereals and cereal products	167.1 (111.5)	1 (3.33)	213.1 (136.9)	0 (0.0)
Pasta and other grains	50.2 (37.0)	1 (3.33)	62.3 (40.4)	0 (0.0)
Rice	7.0 (9.5)	5 (16.67)	5.3 (6.5)	5 (27.78)
Bread	71.9 (73.3)	6 (20.00)	105.9 (100.0)	1 (5.56)
Pizza, crackers, and other salty snacks	38.1 (27.7)	2 (6.67)	39.6 (41.5)	0 (0.0)
Meats and meat products	100.7 (58.8)	0 (0.0)	109.1 (59.3)	0 (0.0)
Red meat	51.0 (45.7)	0 (0.0)	51.4 (40.7)	1 (5.56)
White meat	27.3 (21.8)	0 (0.0)	31.4 (29.6)	0 (0.0)
Processed meat	21.4 (17.3)	0 (0.0)	25.4 (23.0)	0 (0.0)
Offal	1.1 (3.1)	22 (73.33)	1.0 (4.0)	17 (94.44)
Milk and dairy products	328.1 (366.5)	0 (0.0)	248.8 (183.6)	0 (0.0)
Milk and yogurt	290.9 (369.8)	4 (13.33)	208.8 (166.9)	4 (22.22)
Milk	213.6 (368.9)	9 (30.00)	172.1 (148.8)	5 (27.78)
Yogurt	77.3 (114.1)	13 (43.33)	36.6 (51.1)	9 (50.00)
Cheese	37.2 (40.2)	0 (0.0)	40.1 (23.3)	0 (0.0)
Fresh cheese	13.8 (16.7)	7 (23.33)	15.1 (9.8)	2 (11.11)
Aged cheese	21.9 (26.3)	1 (3.33)	23.0 (21.4)	0 (0.0)
Eggs	14.9 (13.4)	2 (6.67)	12.9 (8.4)	1 (5.56)
Fish and seafood	29.4 (24.2)	2 (6.67)	33.0 (25.8)	1 (5.56)
Fish	23.6 (19.7)	2 (6.67)	29.6 (24.6)	1 (5.56)
Preserved and tinned fish	10.9 (15.7)	3 (10.00)	15.7 (14.3)	2 (11.11)
Non-piscivorous fish	8.4 (9.4)	7 (23.33)	8.9 (14.3)	3 (16.67)
Piscivorous fish	4.4 (6.3)	11 (36.67)	5.1 (8.0)	7 (38.89)
Crustaceans and molluscs	5.8 (8.2)	6 (20.00)	3.4 (4.5)	7 (38.89)
All vegetables	117.3 (89.8)	0 (0.0)	111.4 (66.5)	0 (0.0)
Leafy vegetables	22.2 (18.2)	0 (0.0)	15.9 (11.9)	0 (0.0)
Tomatoes	40.5 (45.5)	0 (0.0)	41.6 (44.6)	1 (5.56)
Root vegetables	26.3 (30.5)	6 (20.00)	23.1 (23.2)	3 (16.67)
Cabbage	5.0 (8.5)	8 (26.67)	6.5 (9.4)	3 (16.67)
Other vegetables	23.3 (19.9)	2 (6.67)	24.2 (22.3)	0 (0.0)
Mushrooms	2.4 (3.1)	13 (43.33)	1.4 (2.1)	7 (38.89)
Legumes	19.3 (18.0)	3 (10.00)	20.2 (18.4)	1 (5.56)

Potatoes	16.5 (16.4)	2 (6.67)	13.4 (10.6)	1 (5.56)
Fresh fruit	245.2 (169.7)	0 (0.0)	261.9 (155.1)	0 (0.0)
Citrus fruit	38.0 (37.7)	3 (10.00)	51.3 (34.8)	2 (11.11)
All other fruit	207.2 (144.0)	2 (6.67)	210.5 (132.0)	0 (0.0)
Dry fruits, nuts and seeds	3.3 (5.1)	5 (16.67)	1.4 (2.1)	0 (0.0)
Dry fruits	0.6 (1.6)	18 (60.00)	0.3 (0.6)	7 (38.89)
Nuts and seeds	2.8 (4.1)	5 (16.67)	1.0 (2.0)	0 (0.0)
Sweets, chocolate, cakes, etc.	133.0 (97.7)	1 (3.33)	129.1 (58.3)	0 (0.0)
Sugar, non-chocolate confectionery	33.3 (47.3)	5 (16.67)	24.3 (26.9)	3 (16.67)
Chocolate, candy bars, etc.	3.9 (6.2)	12 (40.00)	3.9 (4.6)	5 (27.78)
Ice-cream	23.2 (33.0)	4 (13.33)	21.4 (15.4)	2 (11.11)
Cakes, pies and pastries	52.3 (53.2)	5 (16.67)	60.3 (41.3)	2 (11.11)
Biscuits, dry cakes	20.4 (21.1)	6 (20.00)	19.1 (29.2)	5 (27.78)
Oils and fats	21.8 (12.4)	1 (3.33)	21.3 (11.2)	0 (0.0)
Vegetable fats and non-olive oils	1.8 (2.5)	9 (30.00)	1.8 (2.1)	7 (38.89)
Olive oil	18.0 (11.4)	1 (3.33)	17.4 (10.3)	1 (5.56)
Butter and other animal fats	2.1 (2.8)	5 (16.67)	2.1 (3.9)	5 (27.78)
Beverages				
Coffee and tea	150.0 (191.7)	4 (13.33)	65.9 (55.8)	4 (22.22)
Coffee	77.8 (82.4)	8 (26.67)	62.8 (53.1)	4 (22.22)
Tea	72.1 (177.4)	19 (63.33)	3.1 (7.3)	15 (83.33)
Wine	72.7 (125.1)	18 (60.00)	111.3 (170.8)	8 (44.44)
Red wine	51.9 (109.9)	20 (66.67)	31.8 (56.4)	11 (61.11)
White wine	20.8 (40.3)	21 (70.00)	79.5 (161.6)	10 (55.56)
Aperitif wines and beers	16.0 (46.2)	21 (70.00)	24.7 (93.7)	10 (55.56)
Spirits and liqueurs	0.1 (0.5)	27 (90.00)	0.1 (0.2)	16 (88.89)
Fruit juices	100.9 (176.0)	9 (30.00)	117.6 (192.5)	8 (44.44)
Soft drinks	39.2 (87.8)	19 (63.33)	22.6 (53.1)	13 (72.22)
Alcohol intake	8.0 (12.7)	6 (20.00)	14.8 (29.1)	2 (11.11)

Table 19. *Food and beverages mean (standard deviation - SD) intake and number (%) of consumers according to EOD subtype. Early onset Alzheimer's dementia (EO-AD) and early onset frontotemporal dementia spectrum (EO-FTD).*

In **Table 20**, we report risk estimates associated with increasing tertiles of food and beverage intake. About overall cereals products, we found an inverse association with EOD risk, although a positive association can be noted for subjects in the third tertile for both pasta and rice consumption. For meat products, we found a direct association with EOD, with higher risk in the second tertile compared to the third one. In the subgroup analyses, however, red, white and processed meat showed a very imprecise inverse association in the second tertile, but a null/positive association in the third tertile. On the other hand, offal intake seemed inversely associated with EOD risk, especially for subjects in the third tertile. Milk and dairy products were in general positively associated with EOD, particularly in the third tertile of exposure. Both piscivorous and non-piscivorous fish seemed inversely associated with EOD risk. For preserved and tinned fish, crustaceans and mollusks, conversely, we found an inverse association in the second tertile, but a positive one in the third tertile. In general, vegetables were inversely associated with EOD risk, particularly leafy, root and other vegetables as well as mushrooms and potatoes, and an almost substantial null association for legumes. As regards fruits, we found an inverse association for fresh fruits, especially citrus fruits,

as well as dry fruits. Conversely, intake of all other fruits showed a negative association in the second tertile and positive one in the third tertile. For overall sweets, we found a positive association with EOD risk, mainly due to ice-cream, cakes, pies/pastries and biscuits/dry cakes, while chocolate and other (non-chocolate) confectionery showed an inverse association. Overall, oils and fats showed an inverse association, mainly due to intake of olive and non-olive oils, while we found a positive association with butter and other animal fats. As concerns beverages, coffee and tea, aperitif wines/beers and spirits/liqueurs showed an inverse association with EOD risk. Red wine showed an inverse association for subjects in the second tertile, and a positive one in the third tertile. Conversely, white wine and soft drinks showed a higher risk in the second tertile and lower one in the third tertile. Finally, fruit juices seemed positively associated with disease risk, especially in the second tertile.

In general, we found similar results in the analysis based on EOD diagnosis, with a few exceptions (**Table 20**). Bread intake was inversely associated with EOD risk and this was also true for EO-AD. However, a direct/null association is present in EOFDT. Fresh cheese intake showed a positive association with EO-FTD, but a null association for EO-AD. Conversely, aged cheese intake did not show such association with EO-FTD and a slight positive association emerged for EO-AD in the third tertile of exposure. With regard to fish intake, EO-FTD showed a positive association with preserved and tinned fish, while an inverse one can be noted for EO-AD. As regards fresh fruit intake, both EO-AD and EO-FTD showed an inverse association, but we found a positive association for citrus fruit in EO-FTD and a negative one in EO-AD. In relation to sweet intake, the increased risk for biscuits and dry cakes was confirmed in EO-AD, while we found a decreased risk for EO-FTD. Finally, alcohol intake was associated with a slightly increased risk in EO-FTD, but not in EO-AD.

		All EOD			EO-AD			EO-FTD		
Food items	**Median**	**Cases/ controls**	**OR[a]**	**(95% CI)**	**Cases/ controls**	**OR[a]**	**(95% CI)**	**Cases/ controls**	**OR[a]**	**(95% CI)**
Cereals and cereal products										
1st tertile (ref.)	90.1	21/18	1.00	-	14/18	1.00	-	6/18	1.00	-
2nd tertile	154.0	7/18	0.30	(0.09–0.96)	3/18	0.18	(0.04–0.81)	3/18	0.38	(0.07–2.04)
3rd tertile	231.5	26/18	0.80	(0.27–2.38)	13/18	0.56	(0.15–2.02)	9/18	0.75	(0.16–3.40)
Linear trend (10g increase)			*1.01*	*(0.96–1.06)*		*0.98*	*(0.92–1.05)*		*1.04*	*(0.98–1.11)*
Pasta and other grains										
1st tertile (ref.)	12.8	12/17	1.00	–	9/17	1.00	–	3/17	1.00	–
2nd tertile	32.2	10/19	0.74	(0.24–2.25)	6/19	0.59	(0.17–2.11)	3/19	0.78	(0.13–4.76)
3rd tertile	80.1	32/18	2.57	(0.87–7.55)	15/18	1.58	(0.45–5.49)	12/18	3.48	(0.72–16.86)
Linear trend (10g increase)			*1.15*	*(1.00–1.32)*		*1.09*	*(0.92–1.29)*		*1.17*	*(0.97–1.40)*
Rice										
1st tertile (ref.)	0.5	23/25	1.00	–	12/25	1.00	–	10/25	1.00	–
2nd tertile	4.0	11/15	0.78	(0.28–2.15)	7/15	0.95	(0.29–3.11)	2/15	0.24	(0.04–1.42)
3rd tertile	8.4	20/14	1.45	(0.56–3.77)	11/14	1.68	(0.55–5.15)	6/14	0.81	(0.21–3.04)
Linear trend (10g increase)			*1.86*	*(0.94–3.97)*		*1.98*	*(0.94–4.20)*		*1.47*	*(0.49–4.37)*
Linear increase (1g increase)			*1.06*	*(0.99–1.14)*		*1.07*	*(0.99–1.15)*		*1.04*	*(0.93–1.16)*
Bread										
1st tertile (ref.)	17.2	21/18	1.00	–	15/18	1.00	–	5/18	1.00	–
2nd tertile	58.6	15/18	0.80	(0.30–2.16)	6/18	0.48	(0.14–1.60)	6/18	1.40	(0.33–5.84)
3rd tertile	111.7	18/18	0.63	(0.22–1.82)	9/18	0.47	(0.14–1.54)	7/18	1.02	(0.24–4.39)
Linear trend (10g increase)			*1.02*	*(0.96–1.08)*		*0.99*	*(0.92–1.07)*		*1.06*	*(0.98–1.15)*
Pizza, crackers, and other salty snacks										

1st tertile (ref.)	19.2	29/18	1.00	–	16/18	1.00	–	10/18	1.00	–
2nd tertile	45.8	11/18	0.30	(0.11–0.84)	4/18	0.18	(0.05–0.73)	5/18	0.42	(0.10–1.68)
3rd tertile	73.5	14/18	0.33	(0.12–0.93)	10/18	0.45	(0.14–1.43)	3/18	0.18	(0.03–0.90)
Linear trend (10g increase)			*0.86*	*(0.75–0.99)*		*0.83*	*(0.69–1.01)*		*0.88*	*(0.72–1.06)*
Meats and meat products										
1st tertile (ref.)	38.5	15/18	1.00	–	9/18	1.00	–	5/18	1.00	–
2nd tertile	90.2	19/18	1.37	(0.51–3.68)	11/18	1.18	(0.38–3.71)	6/18	1.16	(0.27–4.96)
3rd tertile	158.6	20/18	1.18	(0.41–3.45)	10/18	0.96	(0.27–3.39)	7/18	1.09	(0.24–4.86)
Linear trend (10g increase)			*1.02*	*(0.94–1.11)*		*1.00*	*(0.91–1.10)*		*1.02*	*(0.90–1.14)*
Red meat										
1st tertile (ref.)	12.4	19/19	1.00	–	11/19	1.00	–	7/19	1.00	–
2nd tertile	46.0	15/17	0.80	(0.29–2.23)	9/17	0.67	(0.20–2.29)	5/17	0.73	(0.17–3.05)
3rd tertile	92.9	20/18	1.04	(0.38–2.86)	10/18	0.81	(0.24–2.71)	6/18	0.75	(0.18–3.21)
Linear trend (10g increase)			*1.01*	*(0.91–1.12)*		*0.99*	*(0.88–1.12)*		*0.98*	*(0.84–1.15)*
White meat										
1st tertile (ref.)	4.9	15/20	1.00	–	9/20	1.00	–	5/20	1.00	–
2nd tertile	18.6	13/17	0.80	(0.28–2.29)	5/17	0.50	(0.13–1.89)	5/17	0.78	(0.17–3.50)
3rd tertile	38.4	26/17	1.85	(0.71–4.84)	16/17	2.08	(0.68–6.32)	8/17	1.47	(0.36–6.01)
Linear trend (10g increase)			*1.12*	*(0.92–1.36)*		*1.15*	*(0.90–1.46)*		*1.15*	*(0.89–1.48)*
Processed meat										
1st tertile (ref.)	6.2	20/18	1.00	–	11/18	1.00	–	7/18	1.00	–
2nd tertile	15.8	11/17	0.51	(0.18–1.47)	6/17	0.54	(0.16–1.87)	4/17	0.60	(0.14–2.64)
3rd tertile	45.0	23/19	0.94	(0.35–2.54)	13/19	1.01	(0.32–3.14)	7/19	0.79	(0.19–3.18)
Linear trend (10g increase)			*0.98*	*(0.78–1.24)*		*0.92*	*(0.69–1.23)*		*1.03*	*(0.75–1.40)*
Offal										
1st tertile (ref.)	0.0	42/42	1.00	–	23/42	1.00	–	17/42	1.00	–
2nd tertile	0.9	8/7	1.28	(0.40–4.07)	4/7	1.17	(0.30–4.67)	0/7	–	–
3rd tertile	8.5	4/5	0.57	(0.13–2.43)	3/5	0.90	(0.19–4.19)	1/5	0.24	(0.02–2.52)
Linear trend (10g increase)			*0.58*	*(0.24–1.42)*		*0.67*	*(0.24–1.88)*		*0.50*	*(0.13–1.95)*
Linear trend (1g increase)			*0.95*	*(0.87–1.04)*		*0.96*	*(0.87–1.07)*		*0.93*	*(0.81–1.07)*
Milk and dairy products										
1st tertile (ref.)	31.1	16/18	1.00	–	7/18	1.00	–	5/18	1.00	–
2nd tertile	149.1	14/18	1.05	(0.37–3.00)	8/18	1.40	(0.38–5.12)	4/18	0.92	(0.17–5.04)
3rd tertile	338.6	24/18	1.25	(0.48–3.25)	15/18	1.92	(0.61–6.05)	9/18	1.45	(0.37–5.67)
Linear trend (10g increase)			*1.02*	*(1.00–1.04)*		*1.03*	*(1.00–1.05)*		*1.02*	*(0.98–1.06)*
Milk and yogurt										
1st tertile (ref.)	17.9	23/25	1.00	–	10/25	1.00	–	8/25	1.00	–
2nd tertile	168.3	12/15	0.85	(0.32–2.28)	10/15	1.67	(0.55–5.12)	1/15	0.17	(0.02–1.61)
3rd tertile	326.4	19/14	1.25	(0.50–3.16)	10/14	1.62	(0.53–4.98)	9/14	1.57	(0.46–5.38)
Linear trend (10g increase)			*1.02*	*(1.00–1.04)*		*1.03*	*(1.00–1.05)*		*1.02*	*(0.98–1.06)*
Milk										
1st tertile (ref.)	0.0	26/28	1.00	–	13/28	1.00	–	8/28	1.00	–
2nd tertile	160.0	11/14	0.73	(0.26–1.06)	8/14	1.27	(0.39–4.12)	2/14	0.35	(0.06–2.15)
3rd tertile	257.7	17/12	1.25	(0.48–3.26)	9/12	1.50	(0.49–4.59)	8/12	1.95	(0.53–7.16)
Linear trend (10g increase)			*1.02*	*(0.99–1.04)*		*1.02*	*(0.99–1.05)*		*1.03*	*(0.99–1.08)*
Yogurt										
1st tertile (ref.)	0.0	29/34	1.00	–	16/34	1.00	–	11/34	1.00	–
2nd tertile	44.6	10/8	1.40	(0.46–4.21)	3/8	0.75	(0.17–3.37)	3/8	1.06	(0.20–5.67)
3rd tertile	125.0	15/12	1.65	(0.64–4.28)	11/12	2.07	(0.72–5.98)	4/12	1.20	(0.30–4.80)
Linear trend (10g increase)			*1.03*	*(0.98–1.08)*		*1.04*	*(0.99–1.10)*		*0.99*	*(0.91–1.08)*
Cheese										
1st tertile (ref.)	10.3	13/18	1.00	–	10/18	1.00	–	2/18	1.00	–
2nd tertile	22.9	16/18	1.03	(0.36–2.90)	9/18	0.78	(0.24–2.51)	5/18	2.51	(0.40–15.71)
3rd tertile	49.6	25/18	1.88	(0.60–5.91)	11/18	0.97	(0.26–3.68)	11/18	7.05	(1.02–48.58)
Linear trend (10g increase)			*1.09*	*(0.91–1.31)*		*1.06*	*(0.89–1.28)*		*1.15*	*(0.85–1.57)*
Linear trend (1g increase)			*1.01*	*(0.99–1.03)*		*1.01*	*(0.99–1.02)*		*1.01*	*(0.98–1.05)*
Fresh cheese										
1st tertile (ref.)	0.8	20/23	1.00	–	13/23	1.00	–	4/23	1.00	–
2nd tertile	8.7	16/16	1.39	(0.53–3.65)	8/16	1.01	(0.33–3.09)	6/16	2.75	(0.60–12.62)
3rd tertile	30.1	15/18	1.47	(0.53–4.12)	9/18	1.00	(0.30–3.41)	8/18	3.88	(0.77–19.58)
Linear trend (10g increase)			*1.06*	*(0.77–1.47)*		*1.03*	*(0.73–1.47)*		*1.21*	*(0.72–2.03)*
Linear trend (1g increase)			*1.01*	*(0.97–1.04)*		*1.00*	*(0.97–1.04)*		*1.02*	*(0.97–1.07)*
Aged cheese										
1st tertile (ref.)	5.6	18/20	1.00	–	11/20	1.00	–	6/20	1.00	–
2nd tertile	12.7	13/17	0.87	(0.32–2.38)	8/17	0.94	(0.30–3.00)	5/17	0.91	(0.21–3.95)
3rd tertile	28.6	23/17	1.37	(0.49–3.79)	11/17	1.15	(0.34–3.87)	7/17	0.91	(0.18–4.47)
Linear trend (10g increase)			*1.11*	*(0.85–1.45)*		*1.11*	*(0.83–1.47)*		*1.09*	*(0.72–1.64)*
Linear trend (1g increase)			*1.01*	*(0.98–1.04)*		*1.01*	*(0.98–1.04)*		*1.01*	*(0.97–1.05)*
Eggs										
1st tertile (ref.)	3.9	21/20	1.00	–	14/20	1.00	–	6/20	1.00	–
2nd tertile	10.4	13/17	0.64	(0.23–1.77)	6/17	0.44	(0.13–1.49)	5/17	1.06	(0.24–4.74)
3rd tertile	23.3	20/17	0.86	(0.31–2.34)	10/17	0.61	(0.19–1.94)	7/17	0.99	(0.24–4.09)
Linear trend (10g increase)			*1.02*	*(0.72–1.43)*		*1.02*	*(0.71–1.48)*		*0.84*	*(0.50–1.41)*

Linear trend (1g increase)			*1.00*	*(0.97–1.04)*		*1.00*	*(0.97–1.04)*		*0.98*	*(0.93–1.04)*
Fish and seafood										
1st tertile (ref.)	9.7	22/20	1.00	–	13/20	1.00	–	6/20	1.00	–
2nd tertile	28.4	18/17	0.98	(0.39–2.48)	9/17	0.83	(0.28–2.48)	7/17	1.40	(0.37–5.30)
3rd tertile	53.9	14/17	0.70	(0.26–1.86)	8/17	0.69	(0.22–2.12)	5/17	0.92	(0.21–3.95)
Linear trend (10g increase)			*0.97*	*(0.82–1.15)*		*0.97*	*(0.80–1.18)*		*1.04*	*(0.81–1.33)*
Fish										
1st tertile (ref.)	8.0	26/21	1.00	–	14/21	1.00	–	9/21	1.00	–
2nd tertile	25.3	13/17	0.58	(0.22–1.51)	9/17	0.79	(0.27–2.31)	2/17	0.24	(0.04–1.32)
3rd tertile	45.3	15/16	0.69	(0.26–1.85)	7/16	0.65	(0.20–2.10)	7/16	0.87	(0.23–3.25)
Linear trend (10g increase)			*0.98*	*(0.80–1.19)*		*0.96*	*(0.75–1.22)*		*1.09*	*(0.83–1.44)*
Preserved and tinned fish										
1st tertile (ref.)	2.0	19/22	1.00	–	12/22	1.00	–	5/22	1.00	–
2nd tertile	8.5	19/18	0.85	(0.32–2.29)	11/18	0.83	(0.26–2.70)	6/18	1.00	(0.23–4.39)
3rd tertile	17.6	16/14	1.22	(0.44–3.36)	7/14	0.88	(0.26–2.95)	7/14	1.88	(0.44–8.11)
Linear trend (10g increase)			*1.29*	*(0.88–1.88)*		*1.19*	*(0.79–1.80)*		*1.96*	*(1.04–3.70)*
Linear trend (1g increase)			*1.03*	*(0.99–1.07)*		*1.02*	*(0.98–1.06)*		*1.07*	*(1.00–1.14)*
Non–piscivorous fish										
1st tertile (ref.)	0.0	26/27	1.00	–	13/27	1.00	–	9/27	1.00	–
2nd tertile	5.7	14/14	0.86	(0.33–2.26)	7/14	0.91	(0.28–2.94)	5/14	0.77	(0.19–3.09)
3rd tertile	16.3	14/13	0.81	(0.29–2.27)	10/13	1.42	(0.45–4.42)	4/13	0.49	(0.10–2.40)
Linear trend (10g increase)			*0.91*	*(0.64–1.28)*		*0.97*	*(0.66–1.45)*		*0.95*	*(0.59–1.53)*
Linear trend (1g increase)			*0.99*	*(0.96–1.03)*		*1.00*	*(0.96–1.04)*		*1.00*	*(0.95–1.04)*
Piscivorous fish										
1st tertile (ref.)	0.0	34/29	1.00	–	20/29	1.00	–	11/29	1.00	–
2nd tertile	6.8	14/13	0.91	(0.35–2.32)	7/13	0.78	(0.25–2.39)	5/13	1.05	(0.28–3.86)
3rd tertile	24.4	6/12	0.48	(0.16–1.49)	3/12	0.36	(0.09–1.49)	2/12	0.58	(0.10–3.27)
Linear trend (10g increase)			*0.72*	*(0.46–1.14)*		*0.62*	*(0.34–1.14)*		*0.79*	*(0.41–1.54)*
Linear trend (1g increase)			*0.97*	*(0.92–1.01)*		*0.95*	*(0.90–1.01)*		*0.98*	*(0.91–1.04)*
Crustaceans and mollusks										
1st tertile (ref.)	0.3	28/26	1.00	–	14/26	1.00	–	11/26	1.00	–
2nd tertile	4.3	9/14	0.59	(0.21–1.65)	7/14	0.93	(0.29–2.96)	2/14	0.27	(0.05–1.55)
3rd tertile	10.6	17/14	1.22	(0.48–3.10)	9/14	1.16	(0.39–3.47)	5/14	1.31	(0.32–5.32)
Linear trend (10g increase)			*0.92*	*(0.55–1.53)*		*1.01*	*(0.58–1.74)*		*0.63*	*(0.20–1.98)*
Linear trend (1g increase)			*0.99*	*(0.94–1.04)*		*1.00*	*(0.95–1.06)*		*0.95*	*(0.85–1.07)*
All vegetables										
1st tertile (ref.)	72.1	29/18	1.00	–	17/18	1.00	–	9/18	1.00	–
2nd tertile	125.1	7/18	0.23	(0.08–0.70)	2/18	0.11	(0.02–0.59)	3/18	0.33	(0.07–1.53)
3rd tertile	189.3	18/18	0.53	(0.21–1.38)	11/18	0.62	(0.21–1.76)	6/18	0.60	(0.16–2.29)
Linear trend (10g increase)			*0.95*	*(0.90–1.00)*		*0.96*	*(0.90–1.01)*		*0.94*	*(0.86–1.02)*
Leafy vegetables										
1st tertile (ref.)	7.1	26/18	1.00	–	13/18	1.00	–	9/18	1.00	–
2nd tertile	18.5	16/18	0.56	(0.21–1.53)	9/18	0.62	(0.19–2.01)	7/18	0.64	(0.16–2.55)
3rd tertile	46.6	12/18	0.43	(0.15–1.19)	8/18	0.55	(0.17–1.80)	2/18	0.20	(0.03–1.19)
Linear trend (10g increase)			*0.82*	*(0.66–1.02)*		*0.87*	*(0.68–1.11)*		*0.66*	*(0.42–1.03)*
Linear trend (1g increase)			*0.98*	*(0.96–1.00)*		*0.99*	*(0.96–1.01)*		*0.96*	*(0.92–1.00)*
Tomatoes										
1st tertile (ref.)	14.2	21/18	1.00	–	14/18	1.00	–	6/18	1.00	–
2nd tertile	38.4	16/18	0.68	(0.26–1.78)	7/18	0.41	(0.12–1.33)	8/18	1.08	(0.27–4.26)
3rd tertile	68.1	17/18	0.74	(0.27–1.97)	9/18	0.60	(0.19–1.90)	4/18	0.51	(0.10–2.47)
Linear trend (10g increase)			*0.95*	*(0.87–1.04)*		*0.95*	*(0.86–1.06)*		*0.94*	*(0.82–1.08)*
Root vegetables										
1st tertile (ref.)	8.2	27/18	1.00	–	15/18	1.00	–	8/18	1.00	–
2nd tertile	21.3	14/18	0.57	(0.21–1.50)	6/18	0.33	(0.09–1.19)	7/18	1.12	(0.29–4.34)
3rd tertile	60.6	13/18	0.47	(0.18–1.27)	9/18	0.53	(0.17–1.65)	3/18	0.37	(0.07–1.95)
Linear trend (10g increase)			*0.89*	*(0.77–1.02)*		*0.91*	*(0.78–1.07)*		*0.85*	*(0.66–1.09)*
Linear trend (1g increase)			*0.99*	*(0.97–1.00)*		*0.99*	*(0.98–1.01)*		*0.98*	*(0.96–1.01)*
Cabbage										
1st tertile (ref.)	0.0	32/31	1.00	–	17/31	1.00	–	10/31	1.00	–
2nd tertile	4.5	12/12	0.90	(0.33–2.41)	7/12	0.89	(0.28–2.82)	5/12	1.26	(0.33–4.74)
3rd tertile	13.6	10/11	0.76	(0.26–2.18)	6/11	0.86	(0.25–2.95)	3/11	0.74	(0.15–3.60)
Linear trend (10g increase)			*0.95*	*(0.58–1.57)*		*0.93*	*(0.51–1.71)*		*1.22*	*(0.62–2.37)*
Linear trend (1g increase)			*1.00*	*(0.95–1.05)*		*0.99*	*(0.93–1.06)*		*1.02*	*(0.95–1.09)*
Other vegetables										
1st tertile (ref.)	9.2	25/18	1.00	–	11/18	1.00	–	9/18	1.00	–
2nd tertile	28.0	18/18	0.81	(0.31–2.11)	13/18	1.29	(0.43–3.88)	5/18	0.68	(0.17–2.70)
3rd tertile	47.4	11/18	0.38	(0.14–1.06)	6/18	0.47	(0.14–1.61)	4/18	0.39	(0.09–1.77)
Linear trend (10g increase)			*0.83*	*(0.68–1.02)*		*0.84*	*(0.66–1.07)*		*0.87*	*(0.65–1.17)*
Linear trend (1g increase)			*0.98*	*(0.96–1.00)*		*0.98*	*(0.96–1.01)*		*0.99*	*(0.96–1.02)*
Mushrooms										
1st tertile (ref.)	0.2	30/24	1.00	–	16/24	1.00	–	12/24	1.00	–
2nd tertile	2.0	9/10	0.63	(0.21–1.90)	4/10	0.57	(0.14–2.22)	4/10	0.57	(0.13–2.54)
3rd tertile	4.0	15/20	0.55	(0.22–1.40)	10/20	0.70	(0.24–2.04)	2/20	0.13	(0.02–0.77)

Linear trend (10g increase)			*0.51*	*(0.11–2.36)*		*0.71*	*(0.12–4.26)*		*0.06*	*(0.00–1.11)*
Linear trend (1g increase)			*0.93*	*(0.80–1.09)*		*0.97*	*(0.83–1.09)*		*0.76*	*(0.57–1.01)*
Legumes										
1st tertile (ref.)	6.2	17/18	1.00	–	10/18	1.00	–	6/18	1.00	–
2nd tertile	17.0	16/18	0.93	(0.35–2.48)	9/18	0.87	(0.27–2.76)	4/18	0.63	(0.14–2.90)
3rd tertile	31.8	21/18	1.27	(0.48–3.31)	11/18	1.08	(0.35–3.32)	8/18	1.35	(0.36–5.07)
Linear trend (10g increase)			*0.93*	*(0.76–1.15)*		*0.92*	*(0.72–1.17)*		*0.94*	*(0.71–1.23)*
Linear trend (1g increase)			*0.99*	*(0.97–1.01)*		*0.99*	*(0.97–1.02)*		*0.99*	*(0.97–1.02)*
Potatoes										
1st tertile (ref.)	5.3	22/18	1.00	–	13/18	1.00	–	7/18	1.00	–
2nd tertile	12.2	15/18	0.54	(0.20–1.45)	7/18	0.40	(0.12–1.36)	7/18	0.70	(0.18–2.79)
3rd tertile	36.0	17/18	0.70	(0.27–1.83)	10/18	0.69	(0.23–2.11)	4/18	0.40	(0.09–1.85)
Linear trend (10g increase)			*0.88*	*(0.69–1.12)*		*0.91*	*(0.69–1.19)*		*0.72*	*(0.44–1.19)*
Linear trend (1g increase)			*0.99*	*(0.96–1.01)*		*0.99*	*(0.96–1.02)*		*0.97*	*(0.92–1.02)*
Fresh fruit										
1st tertile (ref.)	108.3	17/18	1.00	–	10/18	1.00	–	7/18	1.00	–
2nd tertile	218.3	16/18	0.77	(0.28–2.12)	11/18	0.93	(0.29–2.94)	3/18	0.29	(0.05–1.54)
3rd tertile	381.0	21/18	0.97	(0.36–2.58)	9/18	0.74	(0.23–2.38)	8/18	0.68	(0.17–2.64)
Linear trend (10g increase)			*1.00*	*(0.97–1.03)*		*0.99*	*(0.96–1.02)*		*0.99*	*(0.95–1.04)*
Citrus fruit										
1st tertile (ref.)	11.9	21/19	1.00	–	15/19	1.00	–	4/19	1.00	–
2nd tertile	50.0	20/17	0.94	(0.37–2.43)	10/17	0.64	(0.21–1.89)	8/17	2.17	(0.49–9.61)
3rd tertile	97.8	13/18	0.53	(0.19–1.46)	5/18	0.28	(0.08–1.00)	6/18	1.54	(0.32–7.48)
Linear trend (10g increase)			*0.91*	*(0.83–1.00)*		*0.87*	*(0.76–0.99)*		*0.93*	*(0.82–1.07)*
All other fruit										
1st tertile (ref.)	82.7	17/18	1.00	–	9/18	1.00	–	7/18	1.00	–
2nd tertile	174.9	12/18	0.55	(0.19–1.57)	9/18	0.74	(0.22–2.45)	3/18	0.25	(0.05–1.34)
3rd tertile	303.2	25/18	1.23	(0.45–3.35)	12/18	1.12	(0.33–3.74)	8/18	0.63	(0.15–3268)
Linear trend (10g increase)			*1.01*	*(0.98–1.05)*		*1.01*	*(0.97–1.05)*		*1.00*	*(0.95–1.06)*
Dry fruits, nuts and seeds										
1st tertile (ref.)	0.3	31/19	1.00	–	15/19	1.00	–	10/19	1.00	–
2nd tertile	1.6	14/18	0.38	(0.15–1.00)	7/18	0.41	(0.13–1.31)	7/18	0.50	(0.14–1.82)
3rd tertile	8.7	9/17	0.24	(0.08–0.72)	8/17	0.44	(0.14–1.44)	1/17	0.05	(0.00–0.64)
Linear trend (1g increase)			*0.89*	*(0.80–0.98)*		*0.94*	*(0.85–1.05)*		*0.73*	*(0.56–0.97)*
Dry fruits										
1st tertile (ref.)	0.0	29/20	1.00	–	18/20	1.00	–	7/20	1.00	–
2nd tertile	0.1	18/22	0.52	(0.21–1.28)	8/22	0.34	(0.12–1.02)	8/22	1.03	(0.28–3.82)
3rd tertile	1.8	7/12	0.23	(0.06–0.80)	4/12	0.24	(0.06–1.04)	3/12	0.29	(0.05–1.76)
Linear trend (1g increase)			*0.74*	*(0.51–1.07)*		*0.88*	*(0.60–1.27)*		*0.46*	*(0.20–1.05)*
Nuts and seeds										
1st tertile (ref.)	0.2	32/20	1.00	–	15/20	1.00	–	11/20	1.00	–
2nd tertile	1.4	13/15	0.43	(0.16–1.17)	7/15	0.52	(0.16–1.69)	6/15	0.48	(0.12–1.88)
3rd tertile	7.1	9/19	0.23	(0.08–0.68)	8/19	0.43	(0.14–0.36)	1/19	0.06	(0.00–0.62)
Linear trend (1g increase)			*0.89*	*(0.79–1.00)*		*0.94*	*(0.84–1.06)*		*0.74*	*(0.54–1.02)*
Sweets, chocolate, cakes, etc.										
1st tertile (ref.)	32.9	11/18	1.00	–	6/18	1.00	–	2/18	1.00	–
2nd tertile	75.3	15/18	1.47	(0.50–4.38)	9/18	1.53	(0.43–5.50)	5/18	2.67	(0.43–16.45)
3rd tertile	167.8	28/18	2.61	(0.82–8.34)	15/18	2.62	(0.66–10.29)	11/18	5.48	(0.85–35.26)
Linear trend (10g increase)			*1.00*	*(0.96–1.06)*		*1.01*	*(0.96–1.07)*		*0.98*	*(0.91–1.07)*
Sugar, non–chocolate confectionery										
1st tertile (ref.)	3.1	25/25	1.00	–	13/25	1.00	–	8/25	1.00	–
2nd tertile	23.4	13/13	0.85	(0.31–2.30)	6/13	0.82	(0.24 – 2.85)	5/13	0.92	(0.22–3.87)
3rd tertile	43.1	16/16	0.79	(0.30–2.07)	11/16	1.16	(0.40–3.38)	5/16	0.55	(0.13–2.38)
Linear trend (10g increase)			*0.98*	*(0.88–1.09)*		*1.03*	*(0.92–1.15)*		*0.91*	*(0.75–1.11)*
Chocolate, candy bars, etc.										
1st tertile (ref.)	0.0	37/33	1.00	–	21/33	1.00	–	12/33	1.00	–
2nd tertile	5.7	8/10	0.77	(0.26–2.28)	5/10	0.82	(0.24–2.81)	3/10	1.00	(0.20–4.93)
3rd tertile	20.0	9/11	0.83	(0.28–2.49)	4/11	0.61	(0.15–2.42)	3/11	0.94	(0.27–4.76)
Linear trend (10g increase)			*0.70*	*(0.45–1.08)*		*0.69*	*(0.41–1.17)*		*0.71*	*(0.37–1.38)*
Linear trend (1g increase)			*0.96*	*(0.92–1.01)*		*0.96*	*(0.91–1.02)*		*0.97*	*(0.90–1.03)*
Ice–cream										
1st tertile (ref.)	2.5	18/24	1.00	–	12/24	1.00	–	4/24	1.00	–
2nd tertile	10.7	12/15	1.37	(0.48–3.87)	8/15	1.20	(0.38–3.76)	3/15	1.73	(0.30–10.06)
3rd tertile	32.1	24/15	2.69	(1.00–7.22)	10/15	1.41	(0.45–4.47)	11/15	7.35	(1.53–35.38)
Linear trend (10g increase)			*1.15*	*(0.97–1.37)*		*1.12*	*(0.94–1.34)*		*1.20*	*(0.91–1.58)*
Linear trend (1g increase)			*1.01*	*(1.00–1.03)*		*1.01*	*(0.99–1.03)*		*1.02*	*(0.99–1.05)*
Cakes, pies and pastries										
1st tertile (ref.)	6.0	13/22	1.00	–	8/22	1.00	–	3/22	1.00	–
2nd tertile	26.5	11/16	1.26	(0.43–3.66)	6/16	1.09	(0.30–3.88)	4/16	2.43	(0.42–13.96)
3rd tertile	88.5	30/16	3.16	(1.15–8.69)	16/16	2.95	(0.88–9.89)	11/16	5.28	(1.09–25.70)
Linear trend (10g increase)			*0.99*	*(0.93–1.05)*		*0.98*	*(0.91–1.06)*		*0.99*	*(0.91–1.07)*
Biscuits, dry cakes										

1st tertile (ref.)	0.0	24/28	1.00	–	11/28	1.00	–	10/28	1.00	–
2nd tertile	12.0	9/13	1.04	(0.36–3.04)	4/13	0.98	(0.25–3.87)	3/13	0.90	(0.19–4.21)
3rd tertile	30.0	21/13	1.72	(0.63–4.66)	15/13	3.12	(1.02–9.59)	5/13	0.68	(0.15–3.11)
Linear trend (10g increase)			*1.19*	*(0.94–1.51)*		*1.31*	*(0.99–1.75)*		*1.10*	*(0.82–1.47)*
Linear trend (1g increase)			*1.02*	*(0.99–1.04)*		*1.03*	*(1.00–1.06)*		*1.01*	*(0.98–1.04)*
Oils and fats										
1st tertile (ref.)	14.6	25/18	1.00	–	14/18	1.00	–	8/18	1.00	–
2nd tertile	21.9	10/18	0.37	(0.13–1.03)	5/18	0.33	(0.09–1.15)	3/18	0.33	(0.07–1.58)
3rd tertile	35.7	19/18	0.58	(0.21–1.61)	11/18	0.65	(0.21–2.05)	7/18	0.62	(0.59–2.49)
Linear trend (10g increase)			*0.66*	*(0.46–0.97)*		*0.70*	*(0.45–1.07)*		*0.65*	*(0.38–1.12)*
Linear trend (1g increase)			*0.96*	*(0.92–1.00)*		*0.96*	*(0.92–1.01)*		*0.96*	*(0.91–1.01)*
Vegetable fats and non–olive oils										
1st tertile (ref.)	0.0	31/28	1.00	–	21/28	1.00	–	7/28	1.00	–
2nd tertile	2.4	13/12	0.99	(0.37–2.66)	3/12	0.28	(0.07–1.22)	9/12	4.54	(1.10–18.76)
3rd tertile	8.5	10/14	0.77	(0.27–2.21)	6/14	0.62	(0.19–2.08)	2/14	0.89	(0.13–5.99)
Linear trend (10g increase)			*0.39*	*(0.11–1.38)*		*0.39*	*(0.08–1.84)*		*0.42*	*(0.07–2.52)*
Linear trend (1g increase)			*0.91*	*(0.80–1.03)*		*0.91*	*(0.78–1.06)*		*0.92*	*(0.77–1.10)*
Olive oil										
1st tertile (ref.)	9.6	19/18	1.00	–	11/18	1.00	–	4/18	1.00	–
2nd tertile	17.4	15/18	0.72	(0.26–1.94)	8/18	0.65	(0.20–2.10)	7/18	1.61	(0.35–7.32)
3rd tertile	29.1	20/18	0.79	(0.29–2.18)	11/18	0.76	(0.23–2.46)	7/18	1.26	(0.26–5.97)
Linear trend (10g increase)			*0.73*	*(0.50–1.06)*		*0.77*	*(0.50–1.17)*		*0.73*	*(0.43–1.22)*
Linear trend (1g increase)			*0.97*	*(0.93–1.01)*		*0.97*	*(0.93–1.02)*		*0.97*	*(0.92–1.02)*
Butter and other animal fats										
1st tertile (ref.)	0.1	16/22	1.00	–	8/22	1.00	–	7/22	1.00	–
2nd tertile	1.2	24/16	2.22	(0.85–5.80)	14/16	2.41	(0.78–7.45)	8/16	1.61	(0.42–6.19)
3rd tertile	3.4	14/16	1.23	(0.42–3.56)	8/16	1.31	(0.37–4.64)	3/16	0.48	(0.09–2.57)
Linear trend (10g increase)			*0.78*	*(0.26–2.36)*		*0.76*	*(0.20–2.95)*		*0.76*	*(0.16–3.56)*
Linear trend (1g increase)			*0.98*	*(0.87–1.09)*		*0.97*	*(0.85–1.11)*		*0.97*	*(0.83–1.14)*
Beverages										
Coffee and tea										
1st tertile (ref.)	47.9	27/19	1.00	–	13/19	1.00	–	11/19	1.00	–
2nd tertile	90.0	11/17	0.46	(0.17–1.24)	5/17	0.46	(0.13–1.59)	4/17	0.38	(0.09–1.55)
3rd tertile	196.4	16/18	0.56	(0.21–1.46)	12/18	0.93	(0.32–2.70)	3/18	0.18	(0.03–0.97)
Linear trend (10g increase)			*0.99*	*(0.96–1.02)*		*1.01*	*(0.98–1.04)*		*0.85*	*(0.75–0.96)*
Coffee										
1st tertile (ref.)	25.7	22/19	1.00	–	10/19	1.00	–	8/19	1.00	–
2nd tertile	67.8	12/14	0.77	(0.27–2.19)	8/14	1.03	(0.31–3.43)	3/14	0.50	(0.09–2.71)
3rd tertile	100.0	20/21	0.71	(0.29–1.78)	12/21	1.03	(0.35–3.04)	7/21	0.63	(0.18–2.26)
Linear trend (10g increase)			*0.99*	*(0.92–1.06)*		*1.02*	*(0.95–1.10)*		*0.95*	*(0.83–1.08)*
Tea										
1st tertile (ref.)	0.0	40/36	1.00	–	19/36	1.00	–	17/36	1.00	–
2nd tertile	42.9	7/7	0.78	(0.24–2.54)	5/7	1.13	(0.30–4.22)	1/7	0.23	(0.02–2.33)
3rd tertile	150.0	7/11	0.61	(0.19–1.93)	6/11	1.09	(0.31–3.91)	0/11	–	–
Linear trend (10g increase)			*0.99*	*(0.96–1.02)*		*0.99*	*(0.96–1.02)*		*0.68*	*(0.41–1.13)*
Wine										
1st tertile (ref.)	0	33/33	1.00	–	19/33	1.00	–	10/33	1.00	–
2nd tertile	53.6	1/7	0.17	(0.02–1.47)	1/7	0.28	(0.03–2.52)	0/7	–	–
3rd tertile	250.0	20/14	1.31	(0.54–3.16)	10/14	1.35	(0.46–4.00)	8/14	1.60	(0.49–5.21)
Linear trend (10g increase)			*0.99*	*(0.97–1.02)*		*0.99*	*(0.96–1.03)*		*1.00*	*(0.97–1.04)*
Red wine										
1st tertile (ref.)	0.0	38/37	1.00	–	21/37	1.00	–	13/37	1.00	–
2nd tertile	31.7	3/9	0.38	(0.09–1.56)	1/9	0.22	(0.03–1.91)	1/9	0.37	(0.04–3.43)
3rd tertile	125.0	13/8	1.70	(0.58–5.00)	8/8	2.39	(0.67–8.58)	4/8	1.26	(0.28–5.61)
Linear trend (10g increase)			*1.02*	*(0.97–1.08)*		*1.04*	*(0.98–1.11)*		*1.00*	*(0.91–1.10)*
White wine										
1st tertile (ref.)	0.0	38/37	1.00	–	22/37	1.00	–	12/37	1.00	–
2nd tertile	44.6	14/9	1.50	(0.55–4.07)	8/9	1.49	(0.48–4.62)	3/9	1.59	(0.38–6.58)
3rd tertile	236.1	2/8	0.20	(0.04–1.10)	0/8	–	–	2/8	0.61	(0.10–3.73)
Linear trend (10g increase)			*0.99*	*(0.95–1.02)*		*0.95*	*(0.88–1.02)*		*1.00*	*(0.97–1.04)*
Aperitif wines and beers										
1st tertile (ref.)	0.0	44/33	1.00	–	22/33	1.00	–	16/33	1.00	–
2nd tertile	6.8	6/11	0.40	(0.12–1.30)	5/11	0.69	(0.20–2.44)	1/11	0.10	(0.01–1.13)
3rd tertile	94.3	4/10	0.25	(0.06–1.01)	3/10	0.41	(0.08–2.07)	1/10	0.12	(0.01–1.42)
Linear trend (10g increase)			*0.95*	*(0.90–1.01)*		*0.94*	*(0.86–1.02)*		*0.96*	*(0.90–1.03)*
Spirits and liqueurs										
1st tertile (ref.)	0.0	48/36	1.00	–	27/36	1.00	–	16/36	1.00	–
2nd tertile	0.7	5/11	0.28	(0.08–0.96)	2/11	0.19	(0.03–1.07)	2/11	0.29	(0.05–1.76)
3rd tertile	5.3	1/7	0.11	(0.01–1.15)	1/7	0.22	(0.02–2.22)	0/7	–	–
Linear trend (1g increase)			*0.42*	*(0.16–1.09)*		*0.52*	*(0.19–1.41)*		*0.16*	*(0.01–1.88)*
Fruit juices										
1st tertile (ref.)	0.0	30/38	1.00	–	17/38	1.00	–	10/38	1.00	–
2nd tertile	89.3	12/8	2.50	(0.84–7.43)	7/8	2.44	(0.70–8.51)	3/8	2.14	(0.41–11.13)

3rd tertile	272.0	12/8	1.94	(0.66–5.71)	6/8	1.89	(0.51–6.97)	5/8	2.62	(0.60–11.56)
Linear trend (10g increase)			*1.02*	*(0.99–1.04)*		*1.02*	*(0.98–1.05)*		*1.03*	*(0.99–1.07)*
Soft drinks										
1st tertile (ref.)	0.0	43/42	1.00	–	24/42	1.00	–	15/42	1.00	–
2nd tertile	71.4	5/4	1.67	(0.38–7.40)	3/4	1.72	(0.33–9.05)	2/4	1.91	(0.26–13.92)
3rd tertile	400.0	6/8	0.62	(0.18–2.18)	3/8	0.69	(0.15–3.22)	1/8	0.17	(0.01–2.21)
Linear trend (10g increase)			*0.98*	*(0.95–1.01)*		*0.98*	*(0.94–1.02)*		*0.95*	*(0.88–1.02)*
Alcohol										
1st tertile (ref.)	0.3	22/22	1.00	–	13/22	1.00	–	6/22	1.00	–
2nd tertile	3.5	14/16	0.81	(0.30–2.21)	8/16	0.78	(0.25–2.48)	5/16	1.13	(0.27–4.78)
3rd tertile	23.8	16/16	1.04	(0.37–2.93)	9/16	1.01	(0.28–3.65)	7/16	1.37	(0.32–5.79)
Linear trend (1g increase)			*0.99*	*(0.97–1.02)*		*0.99*	*(0.95–1.02)*		*1.01*	*(0.98–1.03)*

Table 20. *Odds Ratio (OR) and 95% confidence intervals (CI) for early onset dementia (EOD), early onset Alzheimer's dementia (EO-AD) and early onset frontotemporal dementia spectrum (EO-FTD) for increasing tertiles of food and beverage intake.*

Moving on to the analysis of adherence to the investigated dietary patterns, cases (overall and both EO-AD and EO-FTD) generally showed slightly lower mean scores (**Table 21**). In the risk analysis according to tertile distribution (**Table 22**), we found a lower EOD risk at increasing adherence in all three dietary patterns, especially for high adherence to MIND dietary patterns.

	Controls	**EOD cases**	**EO-AD cases**	**EO-FTD cases**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
GM diet (range 0-9)	4.4 (1.7)	4.1 (1.5)	4.1 (1.5)	4.1 (1.5)
DASH diet (rang 8-40)	23.7 (5.5)	23.1 (5.0)	23.5 (5.4)	23.6 (4.4)
MIND diet (range 0-15)	7.8 (1.3)	7.1 (1.4)	7.2 (1.4)	7.2 (1.3)

Table 21. *Adherence to dietary patterns (Greek-Mediterranean (GM) diet; DASH: Dietary Approaches to Stop Hypertension (DASH) diet); Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet) in the study population (early onset dementia (EOD), early onset Alzheimer's dementia (EO-AD) and early onset frontotemporal dementia spectrum (EO-FTD). Values reported as mean and standard deviation (SD).*

		All EOD			**EO-AD**			**EO-FTD**		
Food items	**Median**	**Cases/ controls**	**OR**	**(95% CI)**	**Cases/ controls**	**OR**	**(95% CI)**	**Cases/ controls**	**OR**	**(95% CI)**
GM diet										
1st tertile (ref.)	3	24/19	1.00	–	14/19	1.00	–	7/19	1.00	–
2nd tertile	5	18/18	0.76	(0.30–1.96)	10/18	0.73	(0.24–2.17)	6/18	0.87	(0.22–3.35)
3rd tertile	6	12/17	0.45	(0.16–1.26)	6/17	0.40	(0.12–1.35)	5/17	0.60	(0.14–2.61)
Linear trend			*0.84*	*(0.65–1.09)*		*0.84*	*(0.62–1.13)*		*0.83*	*(0.57–1.20)*
DASH diet										
1st tertile (ref.)	18	21/19	1.00	–	10/19	1.00	–	7/19	1.00	–
2nd tertile	25	22/19	0.87	(0.35–2.15)	13/19	1.08	(0.37–3.17)	7/19	0.80	(0.22–3.00)
3rd tertile	29	11/16	0.60	(0.21–1.72)	7/16	0.79	(0.23–2.74)	4/16	0.71	(0.14–3.52)
Linear trend			*0.98*	*(0.90–1.06)*		*0.99*	*(0.91–1.08)*		*1.01*	*(0.89–1.14)*
MIND diet										
1st tertile (ref.)	6.5	30/16	1.00	–	16/16	1.00	–	9/16	1.00	–
2nd tertile	7.5	15/22	0.32	(0.12–0.83)	9/22	0.39	(0.13–1.15)	5/22	0.31	(0.07–1.28)
3rd tertile	9.0	9/16	0.31	(0.11–0.90)	5/16	0.32	(0.09–1.13)	4/16	0.45	(0.10–2.00)
Linear trend			*0.66*	*(0.47–0.91)*		*0.67*	*(0.46–0.98)*		*0.66*	*(0.41–1.08)*

Table 22. *Odds Ratio (OR) and 95% confidence intervals (CI) of early onset dementia (EOD), early onset Alzheimer's dementia (EO-AD) and early onset frontotemporal dementia spectrum (EO-FTD)*

for increasing tertiles of adherence to dietary patterns. Greek-Mediterranean (GM) diet, Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. Linear trend for 1-unit increase reported.

In Figures 12-21, we present data based on the spline regression analysis adjusted for sex, age, educational attainment and total energy intake. Due to the very high number of non-consumers, spline analysis was not feasible for some offal and several beverages, namely tea, red and white wine, aperitif wines and beers, and soft drinks. Overall, cereal products showed a U-shaped relation with EOD, with lower risk at around 200 g/day yet a higher one above 350g/day (**Figure 12**). A similar relation was found for bread and rice intake. Conversely, pasta and other grains showed a linear relation with decreased risk at low intake levels and an increasing one from 50-60 g/day. On the other hand, pizza, crackers and other salty snacks showed increased risk in case of null exposure, with decreased risk from 40 g/day after which a plateau was reached. Overall meat consumption did not seem to be associated with EOD (**Figure 13**), although an increase in risk can be noted for high intake of both red (>100/120 g/day) and white meat (>40/50 g/day). As regards dairy products, we found null/decreased risk for all products, except for an increase in risk at very high intake levels, namely >400 g/day for overall dairy products or >350 g/day for milk and yogurt (**Figure 14**). Similarly, we found null risk in association with the intake of eggs (**Figure 14**) and overall fish and seafood (**Figure 15**). Interestingly, we found a U-shaped relation with fish intake, with increased risk for null consumption and above 20 g/day for preserved and tinned fish (**Figure 15**). Conversely, high intake (>20 g/day) of other fish, especially piscivorous fish, appeared to decreased EOD risk. All vegetables showed an inverse association with EOD, with increased risk in case of null intake and decreasing risk starting from 100 g/day, above which a plateau seems to have been reached (**Figure 16**). Such pattern of association can also be noted in all vegetable subgroups, especially leafy vegetables showing a slight continuous decrease, while cabbages showed a null association at all intake levels. Mushrooms showed a U-shape relation, with lower risk at around 4 g/day. On the other hand, we found a slight inverse association for potatoes and legumes, albeit a very imprecise one (**Figure 17**). In spite of the substantially linear inverse correlation of citrus fruit intake with EOD risk, we found a U-shaped relation with fresh fruit and all other fruit intake, with lower risk at approximately 250 g/day and 200 g/day, respectively (**Figure 18**). Conversely, dry fruit intake showed increased risk for subjects reporting null consumption and a decreased risk from 4 g/day of dry fruits and nuts and from 1 g/day of dry fruits, above which a plateau was reached (**Figure 18**). Sweet products showed an inverse-U relation with EOD risk, mainly driven by the lower risk associated with high intake of chocolate and other chocolate-based products (**Figure 19**). However, sugar and other confectionery showed a null association, while both ice-cream, biscuits and dry cakes showed a positive correlation, with null risk for non-consumers and increased risk for intake above 20-30 g/day for both

ice-cream and dry cakes, respectively (**Figure 19**). In general, oils and fats showed a linear inverse association with increased risk starting from null intake, soon reversed above 20 g/ especially for olive oil and other vegetable oils and fats (**Figure 20**). For beverages, we found a U-shape relation with coffee consumption, with lower risk at 70 g/day (**Figure 21**). Conversely, we found almost null relation with wine and alcohol intake, while risk increased with fruit juice consumption exceeding 100 g/day (**Figure 21**).

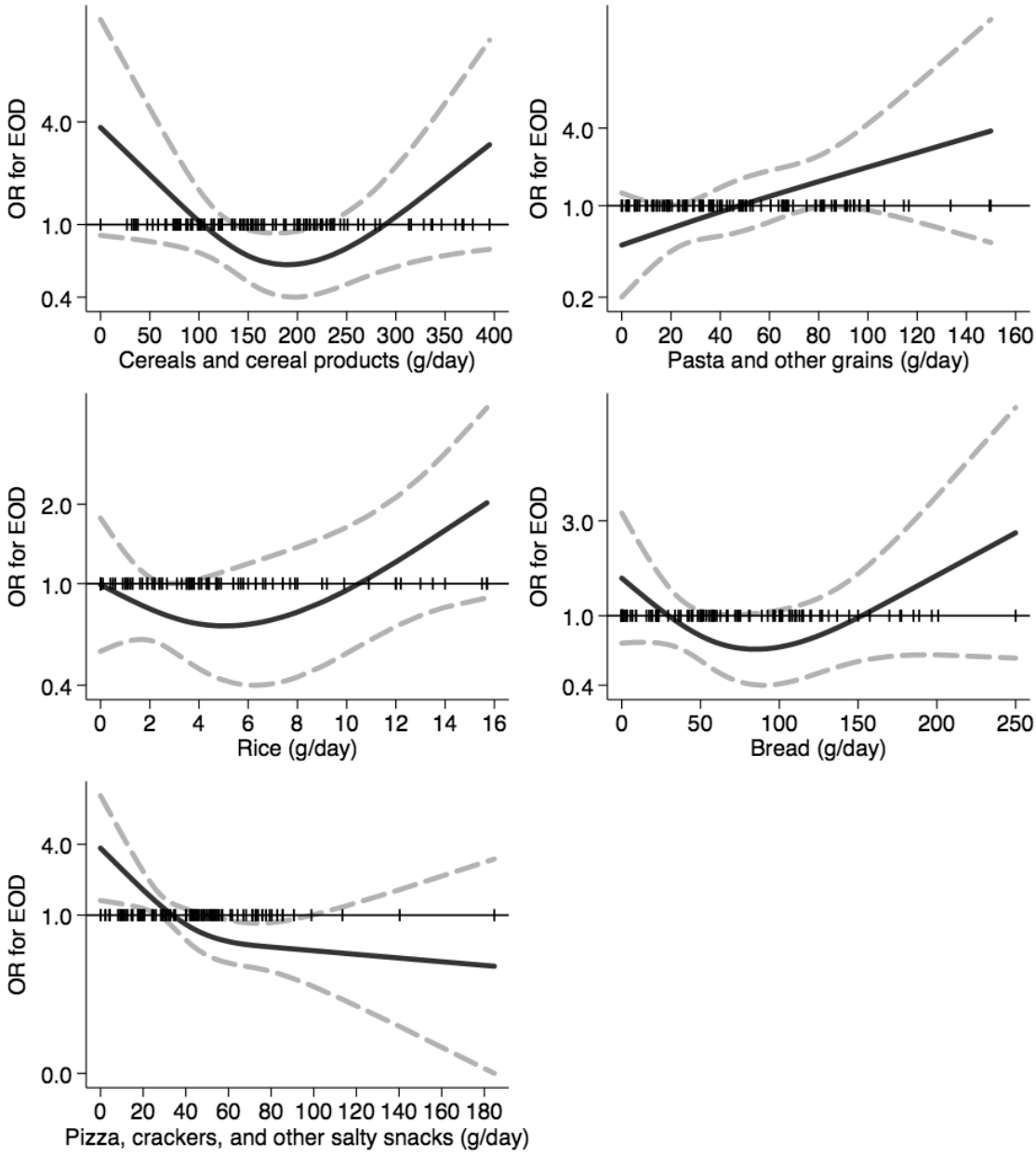


Figure 12. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: cereals and cereal products. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

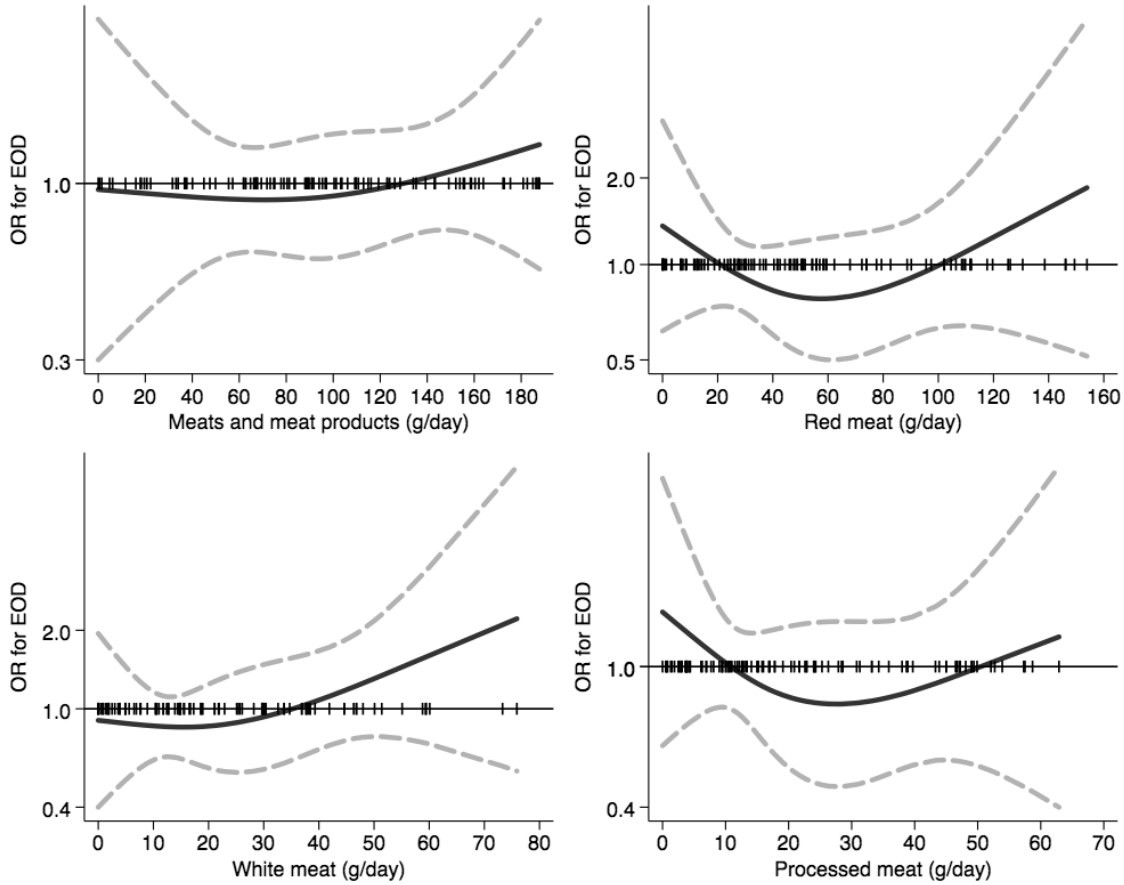


Figure 13. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: meats and meat products. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

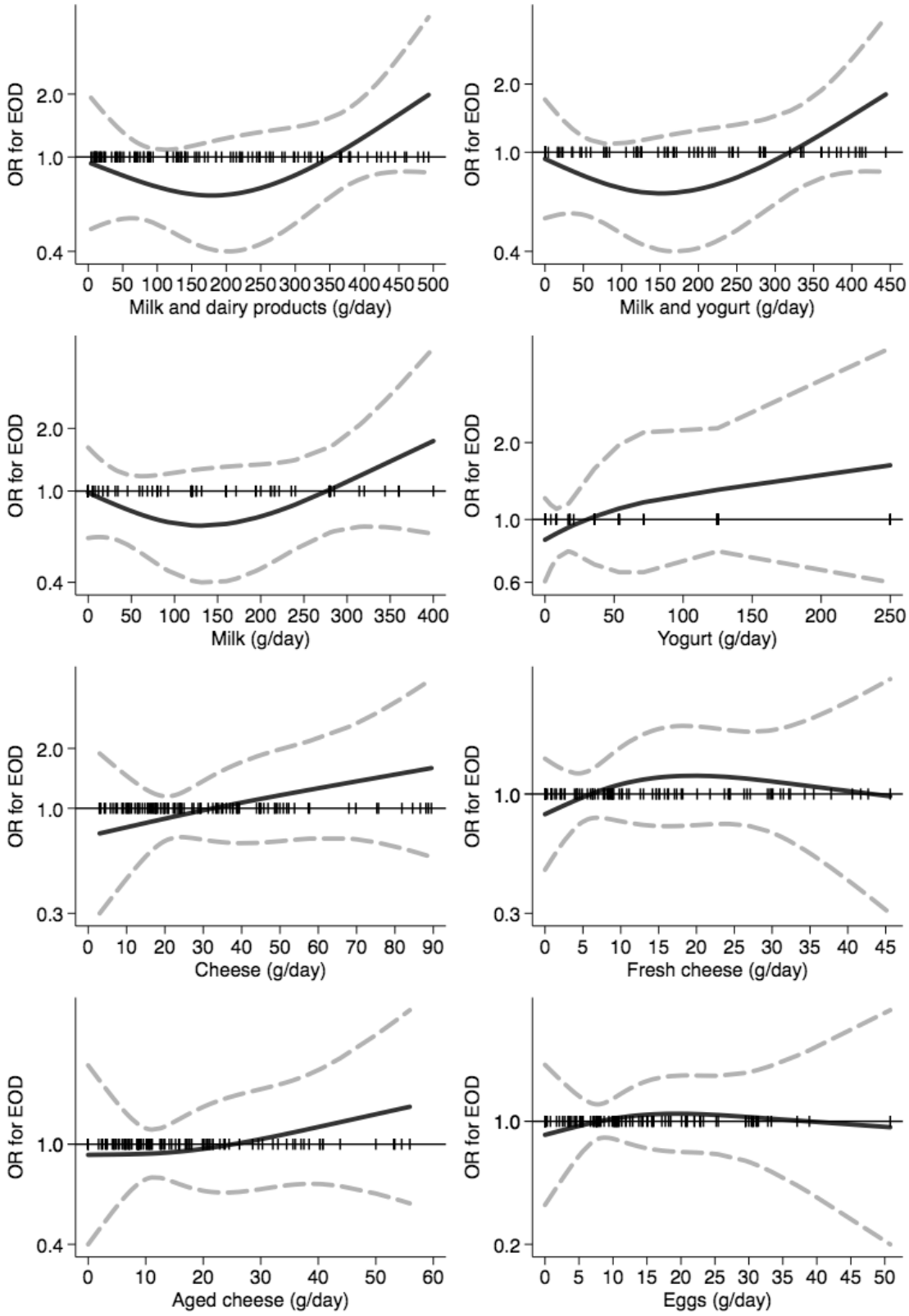


Figure 14. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: milk, dairy products and eggs. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

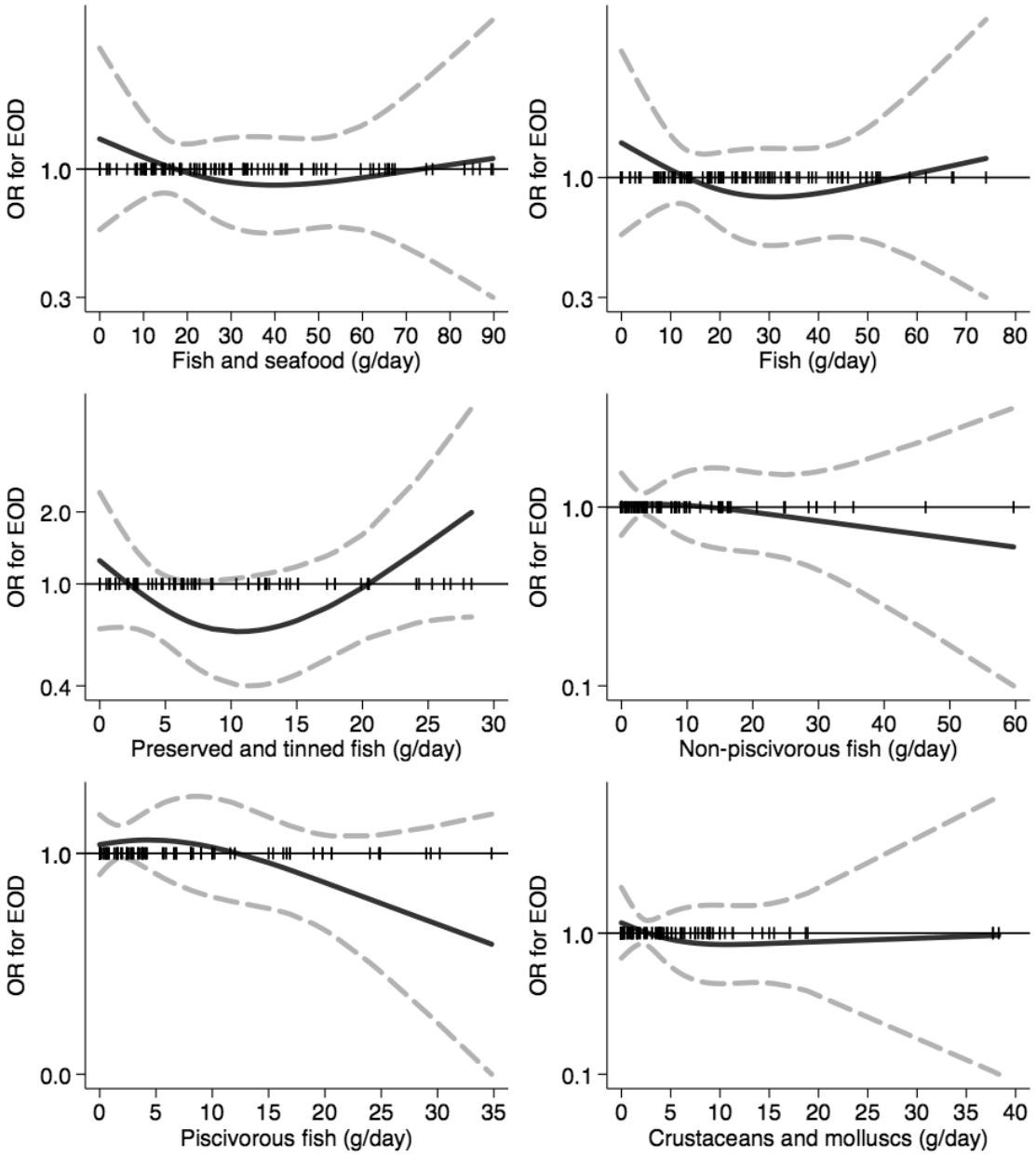


Figure 15. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: fish and seafood. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spike indicates the distribution of participant intake.*

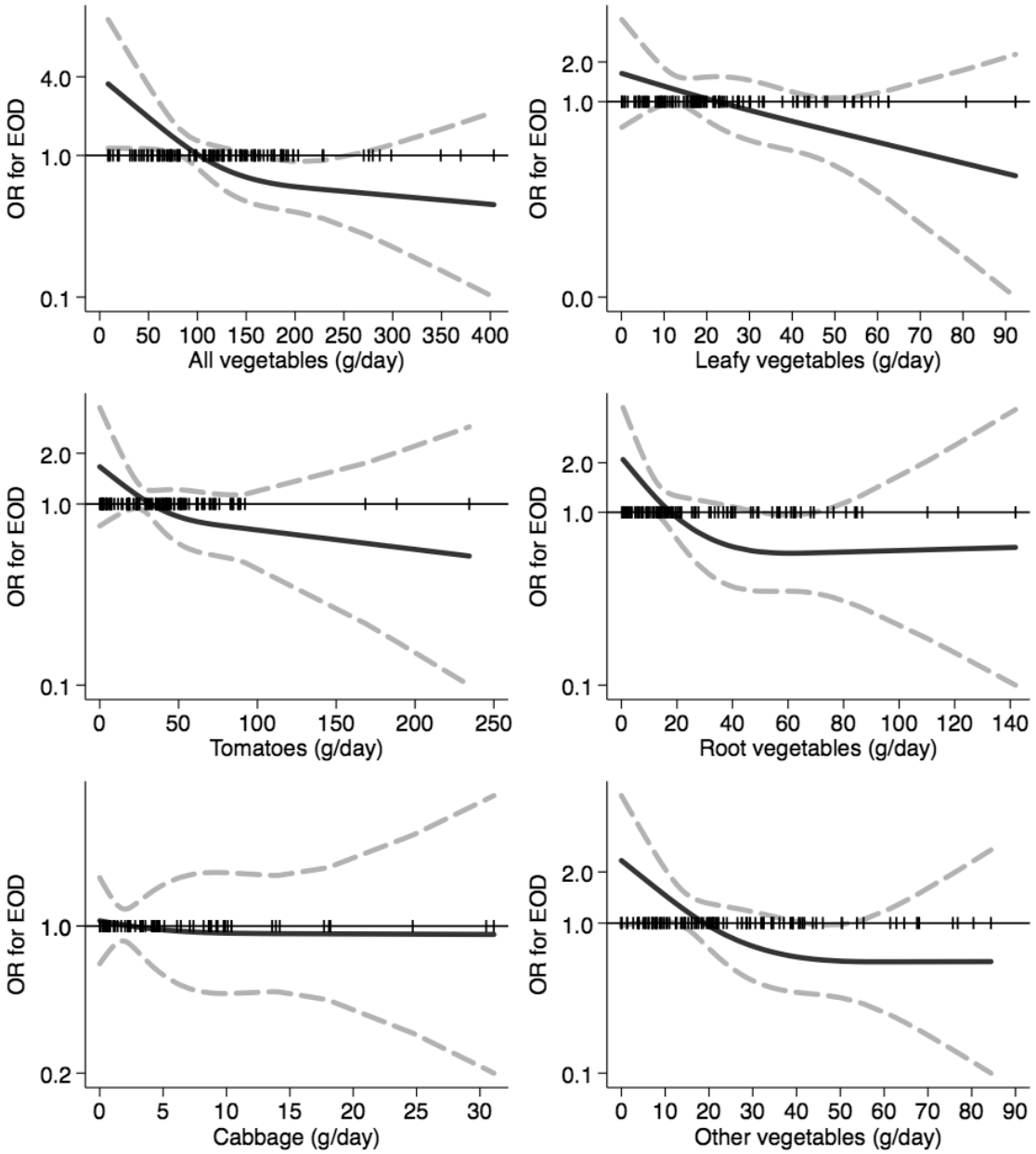


Figure 16. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: vegetables. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicate the distribution of participant intake.*

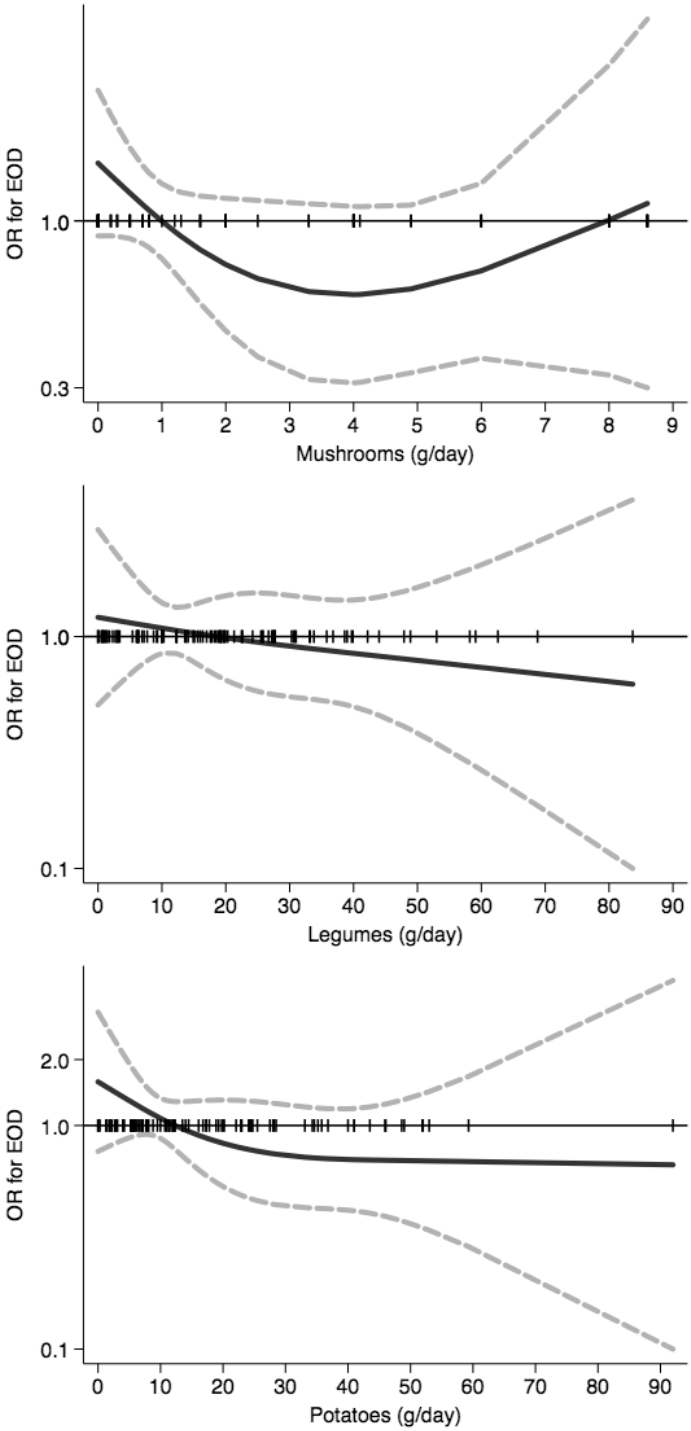


Figure 17. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: mushrooms, legumes and potatoes. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

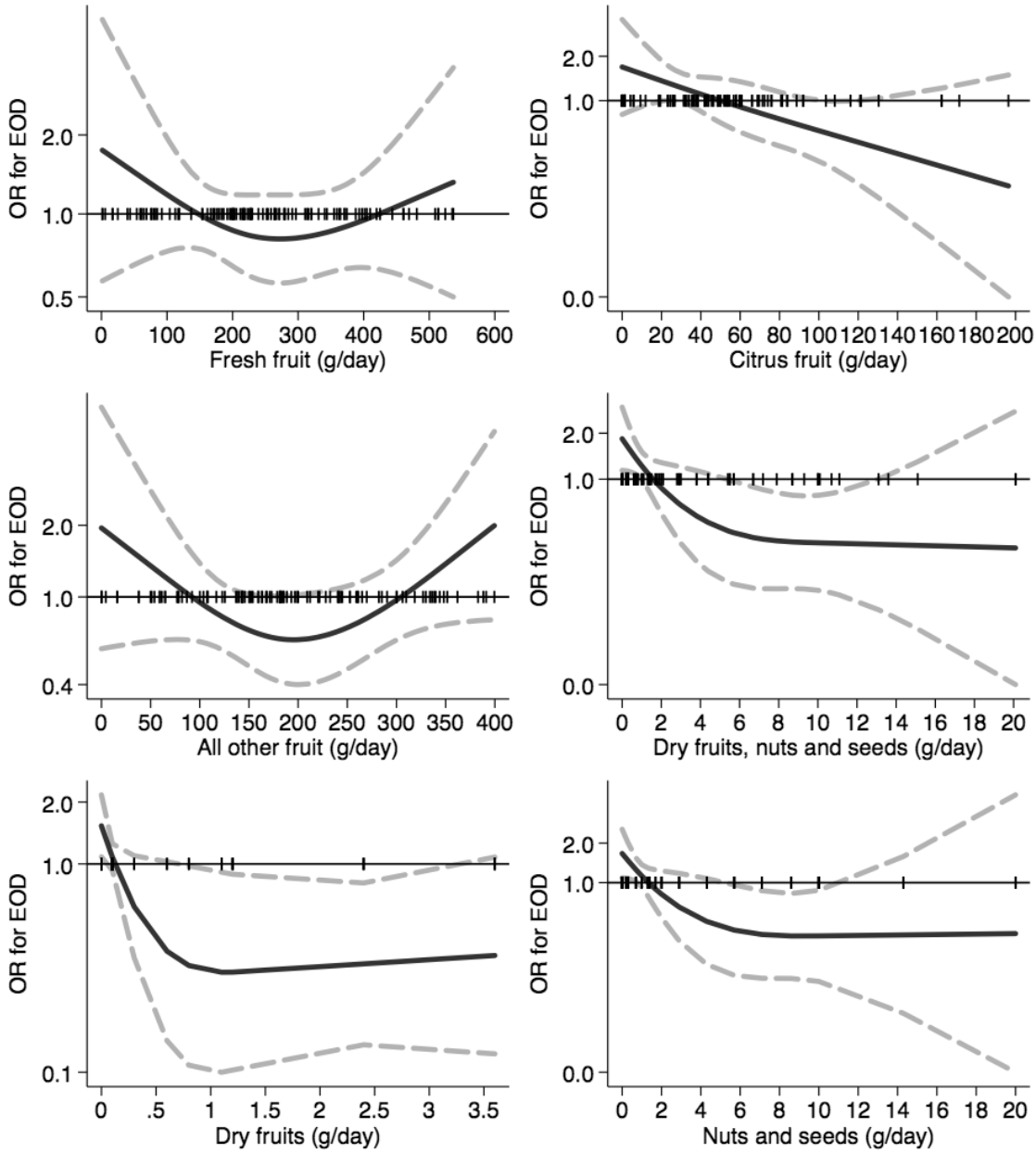


Figure 18. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: fresh and dry fruits. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

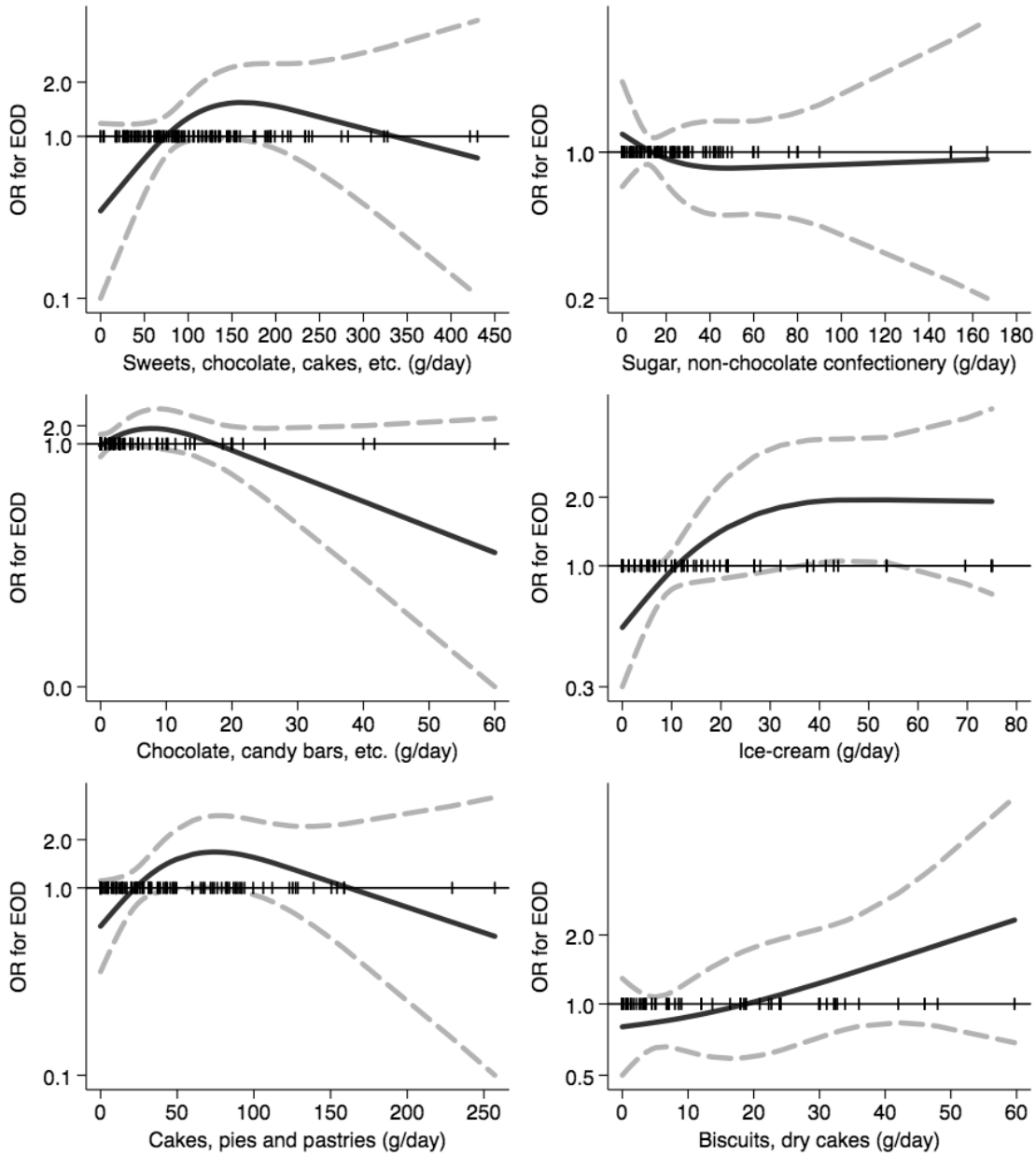


Figure 19. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: sweets, chocolate, cakes, etc. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

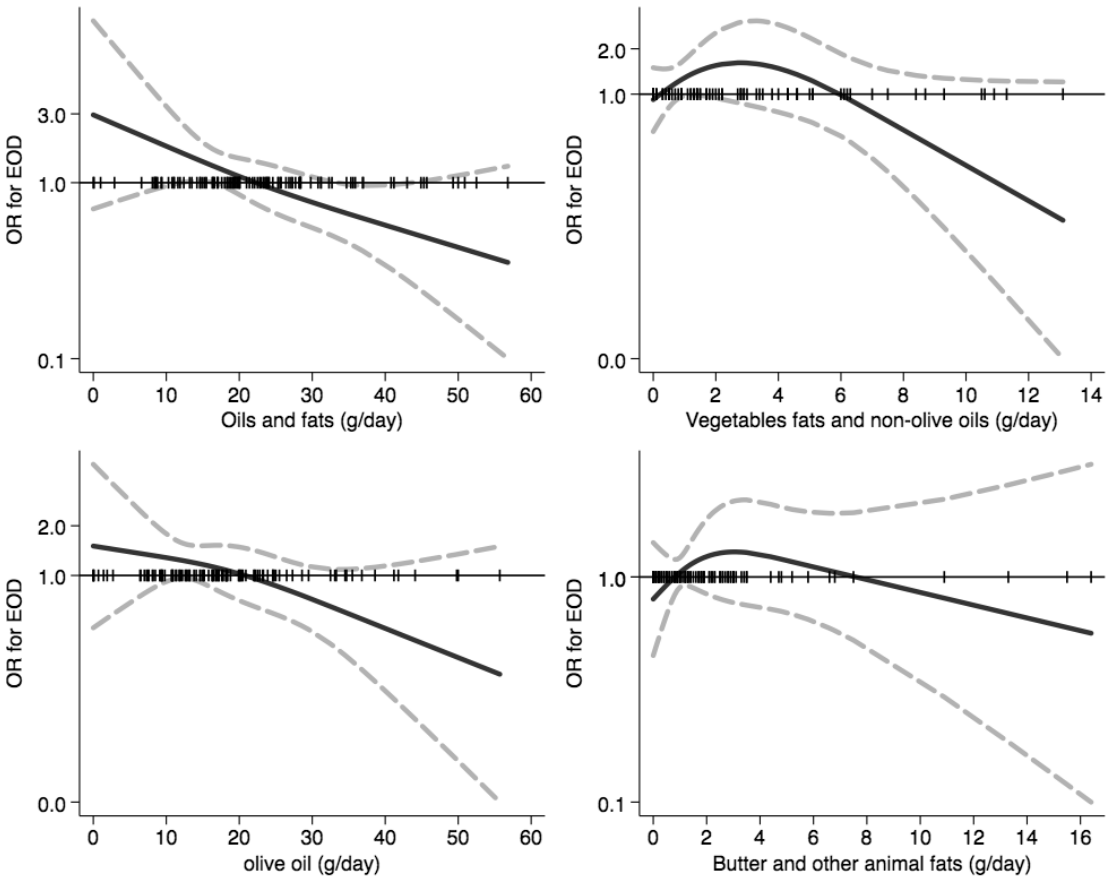


Figure 20. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: oils and fats. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

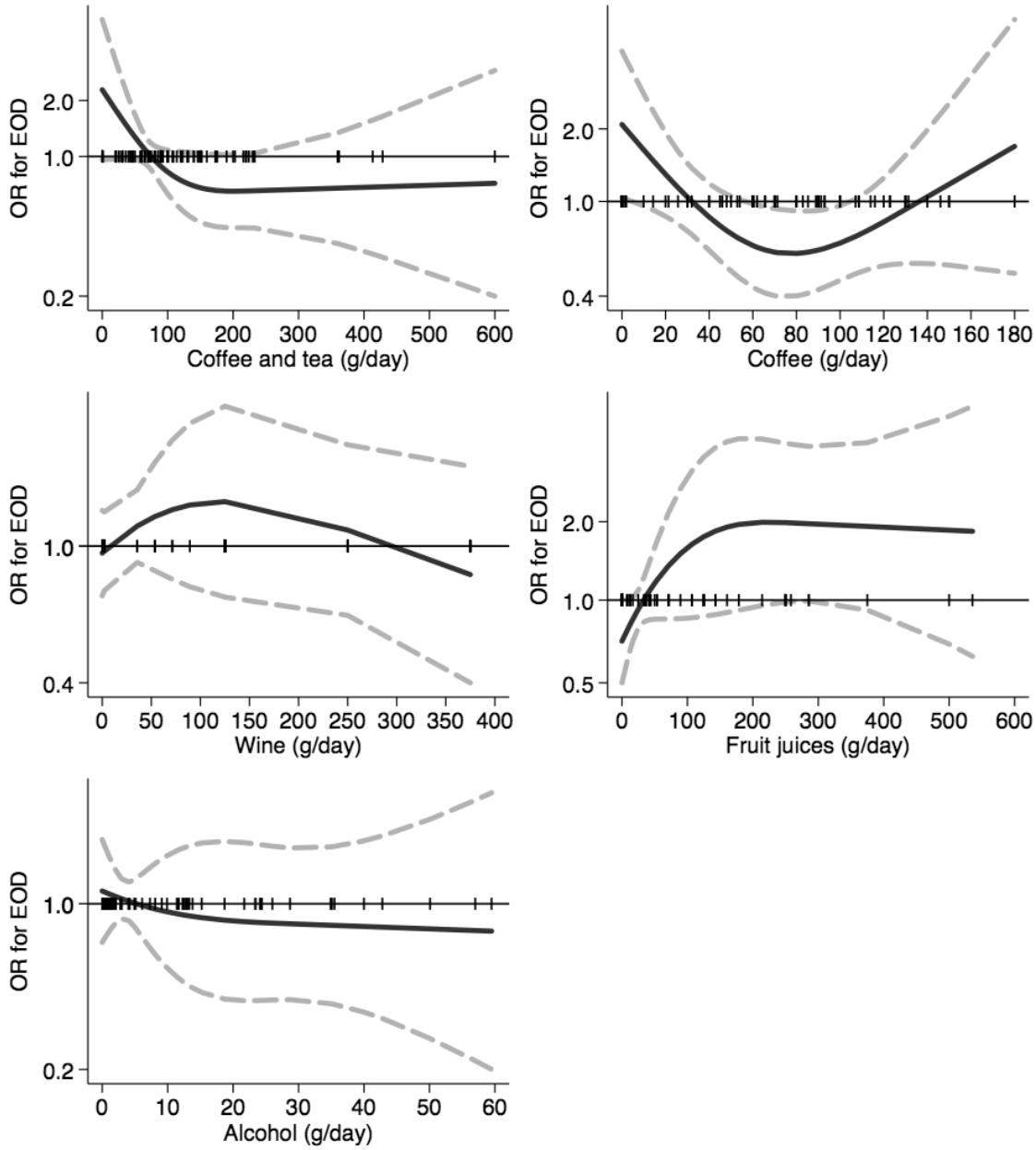


Figure 21. *Spline regression analysis of early onset dementia (EOD) risk for increasing intake of food: beverages. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake. Note: spline analysis was not possible for offal and most of beverages due to few subjects reporting consumption different from a null value (tea, red, white and aperitif wines and beers, spirits and soft drinks).*

Spline regression analyses stratified by EOD clinical type are reported in **Figures 22-31** for EO-AD and in **Figures 32-41** for EO-FTD. We generally found comparable results across EOD forms. Nonetheless, there was evidence of a U-shaped relation between red meat intake and EO-AD (**Figure 23**), and between processed meat and EO-FTD (**Figure 33**), with the lowest risk ratio occurring at 60 g/day and at 25 g/day, respectively.

As regards dairy products, the shape of the relation with cheese intake seemed opposite for EO-AD and EO-FTD, with an inverse U-shaped relation for EO-AD especially for fresh-cheese intake (**Figure 24**), and a U-shaped relation for EO-FTD, especially for overall cheese intake (**Figure 34**). Also, egg intake seemed to establish an inverse-U relation for EO-AD only (**Figure 25**). In addition, mushroom intake showed a linear inverse association for EO-AD (**Figure 27**), and a U-shaped one with EO-FTD (**Figure 37**).

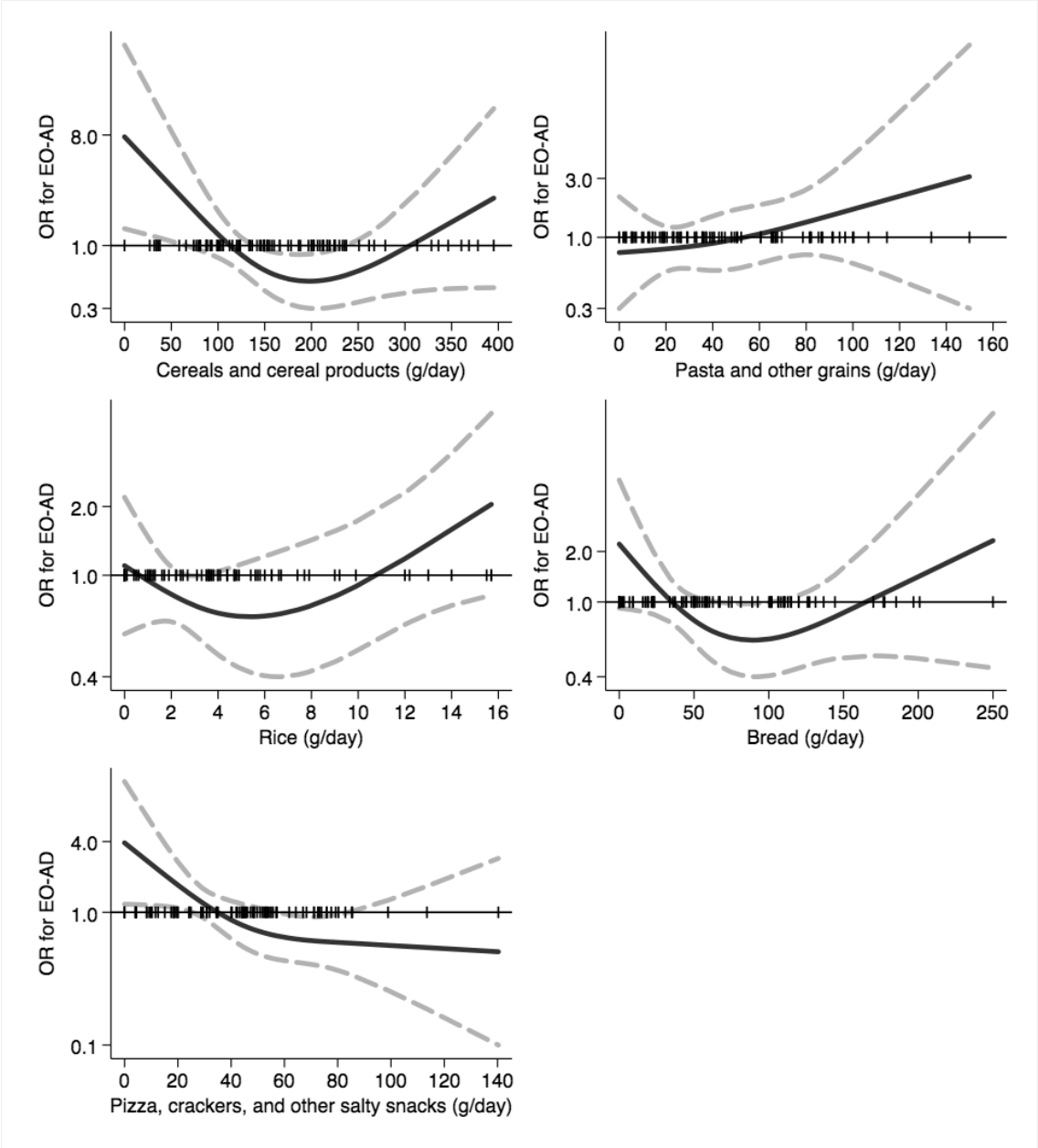


Figure 22. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: cereals and cereal products. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

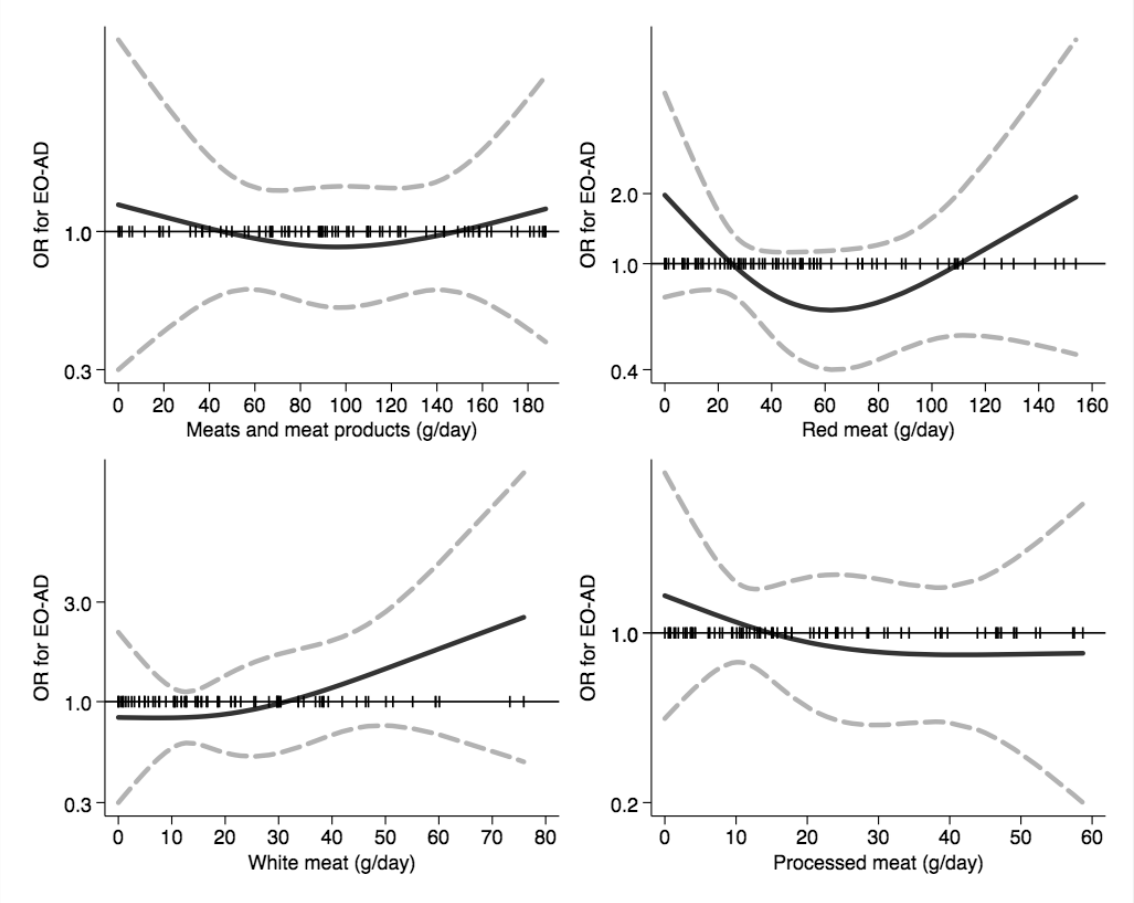


Figure 23. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: meats and meat products. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

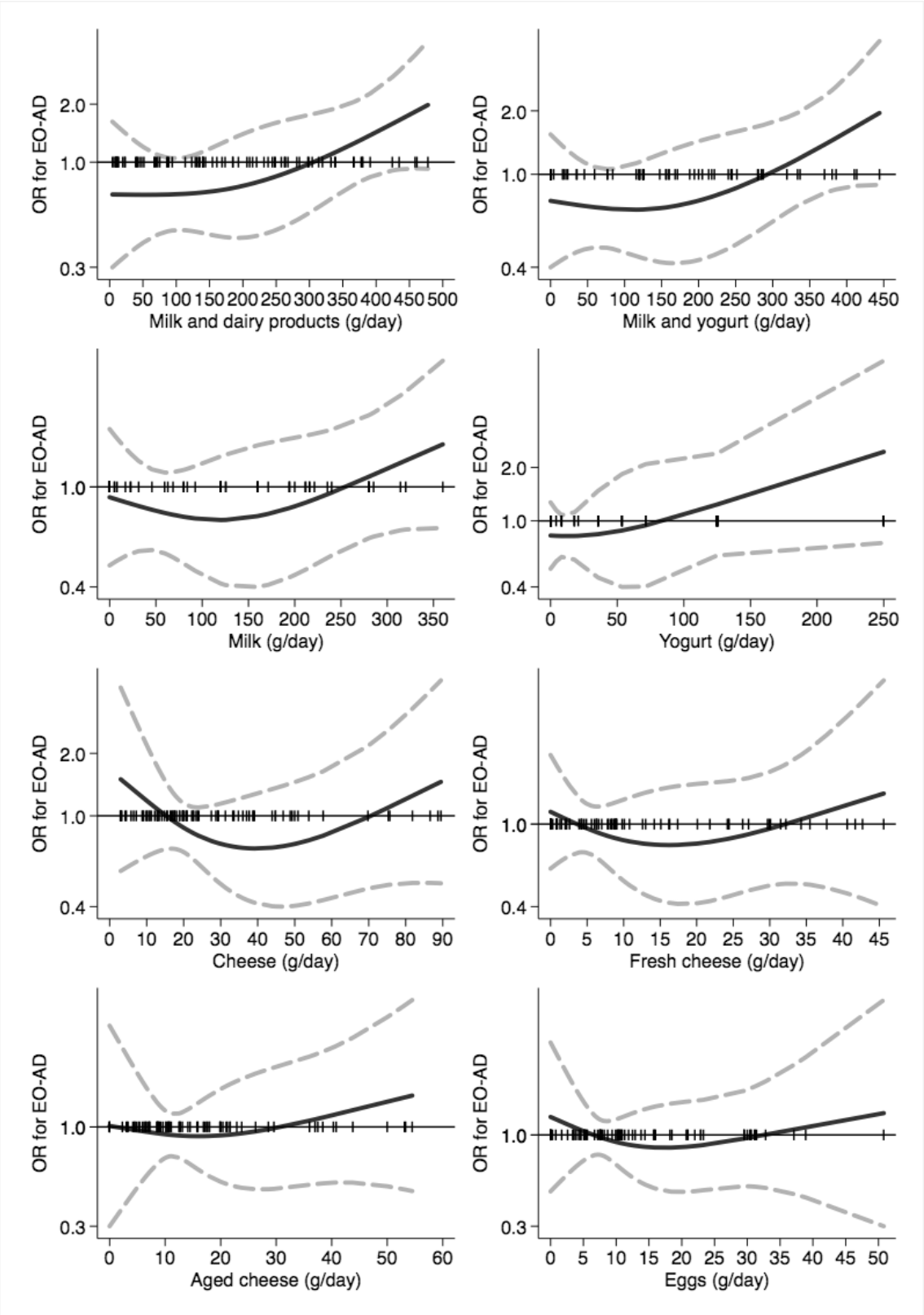


Figure 24. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: milk, dairy products and eggs. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

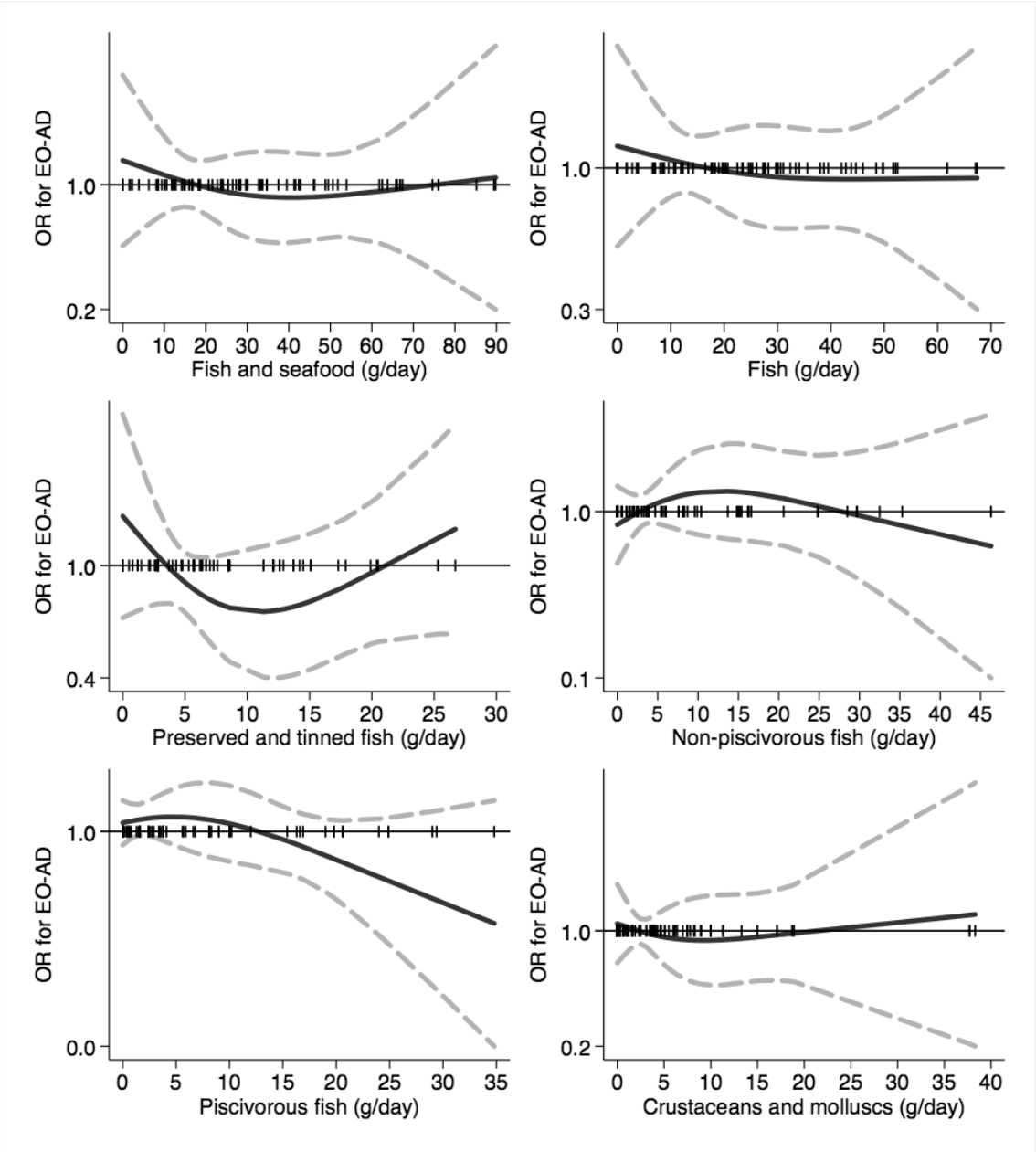


Figure 25. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: fish and seafood. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

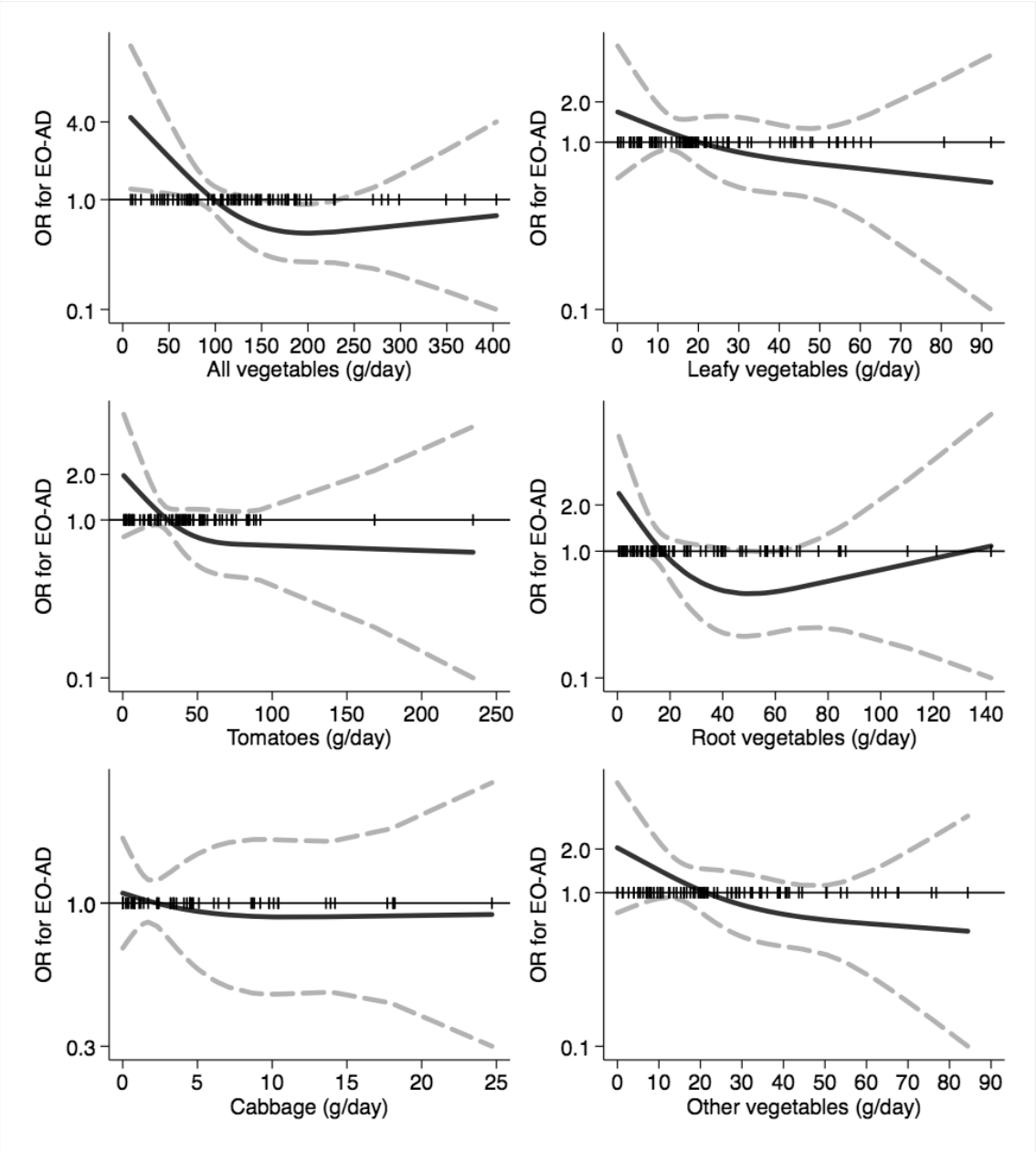


Figure 26. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: vegetables. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

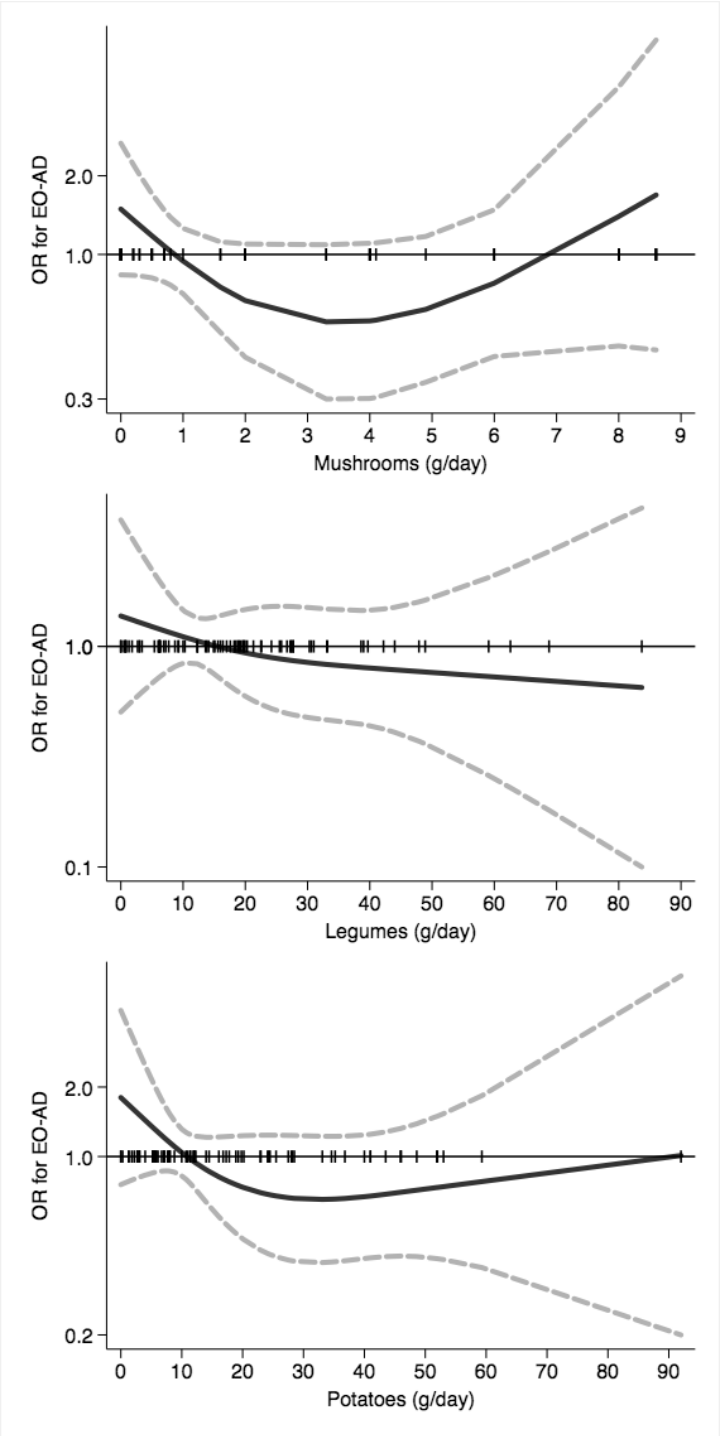


Figure 27. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: mushrooms, legumes and potatoes. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

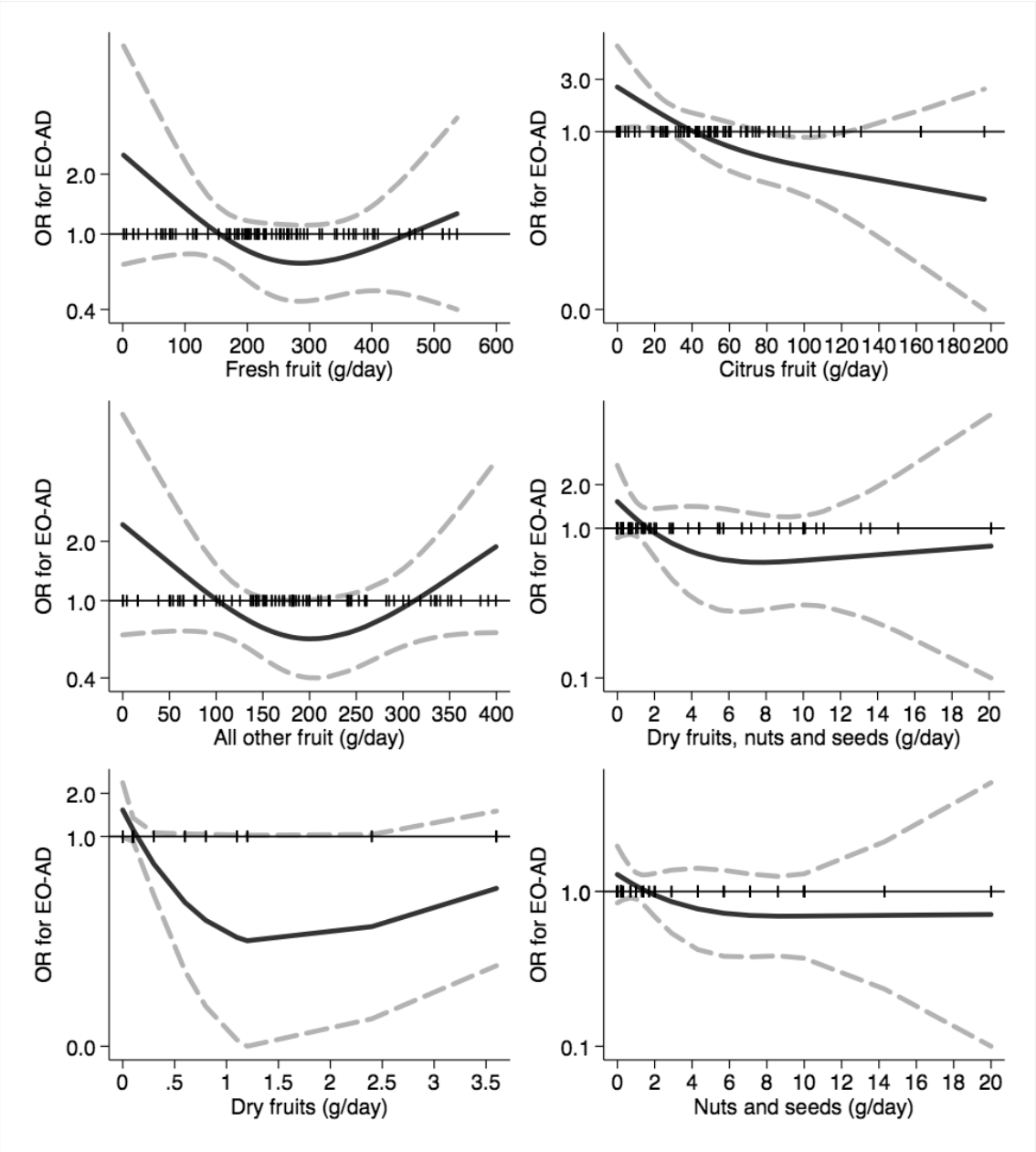


Figure 28. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: fresh and dry fruits. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

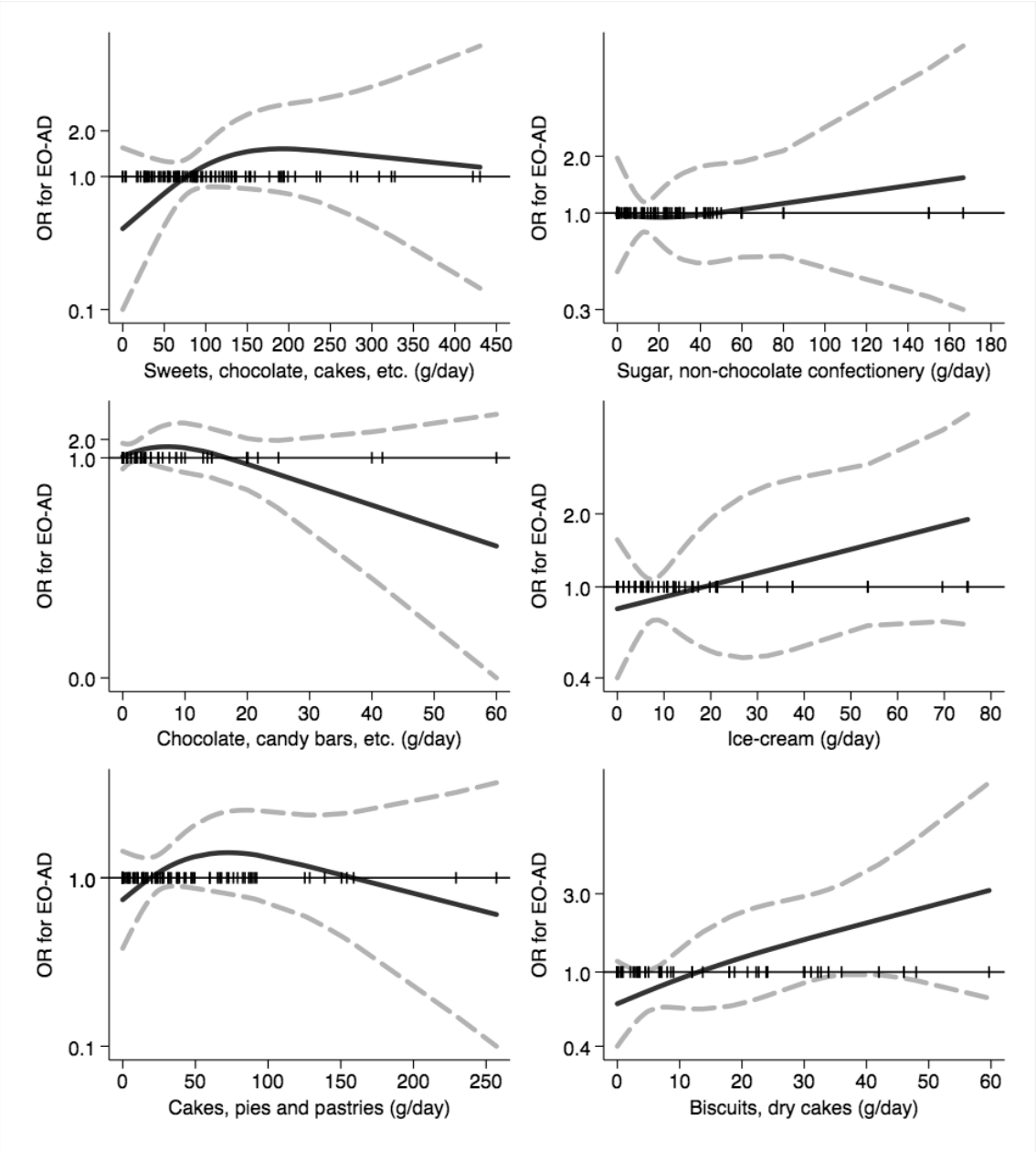


Figure 29. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: sweets, chocolate, cakes, etc. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

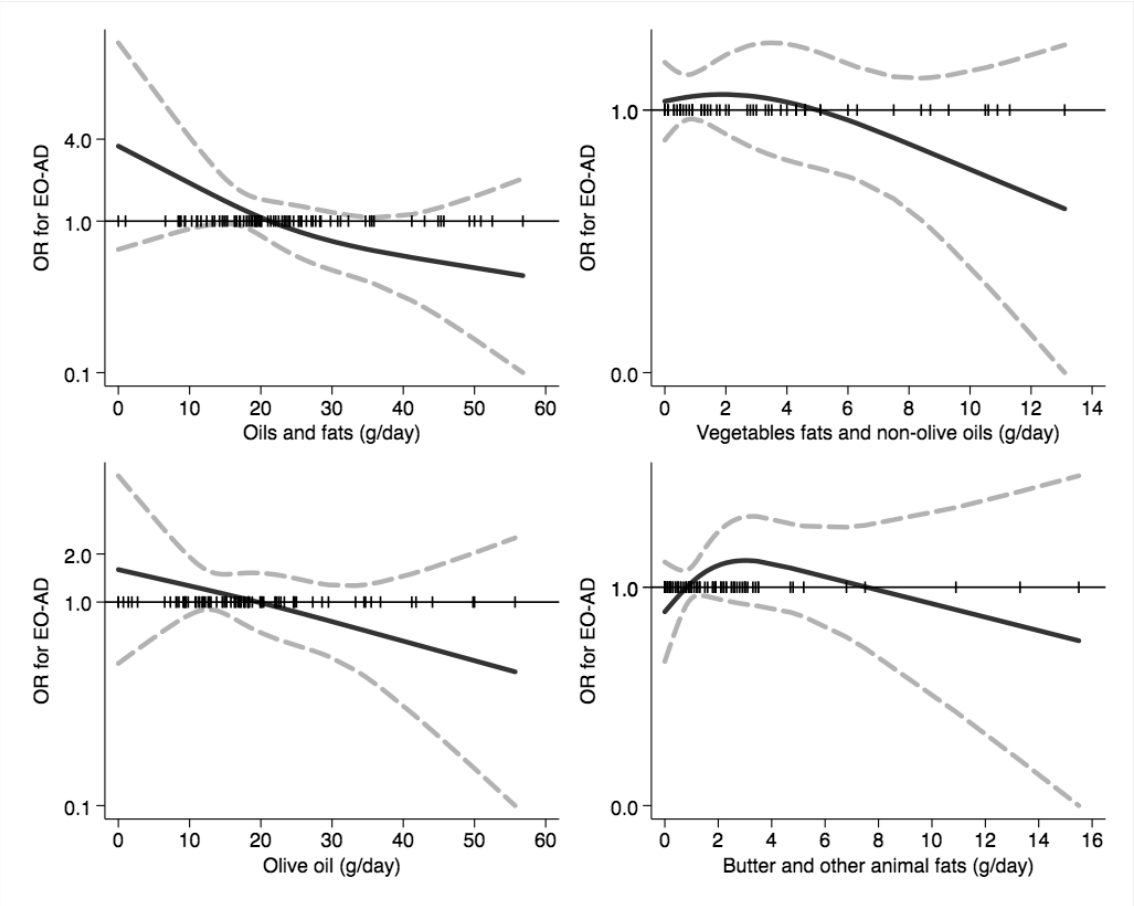


Figure 30. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: oils and fats. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

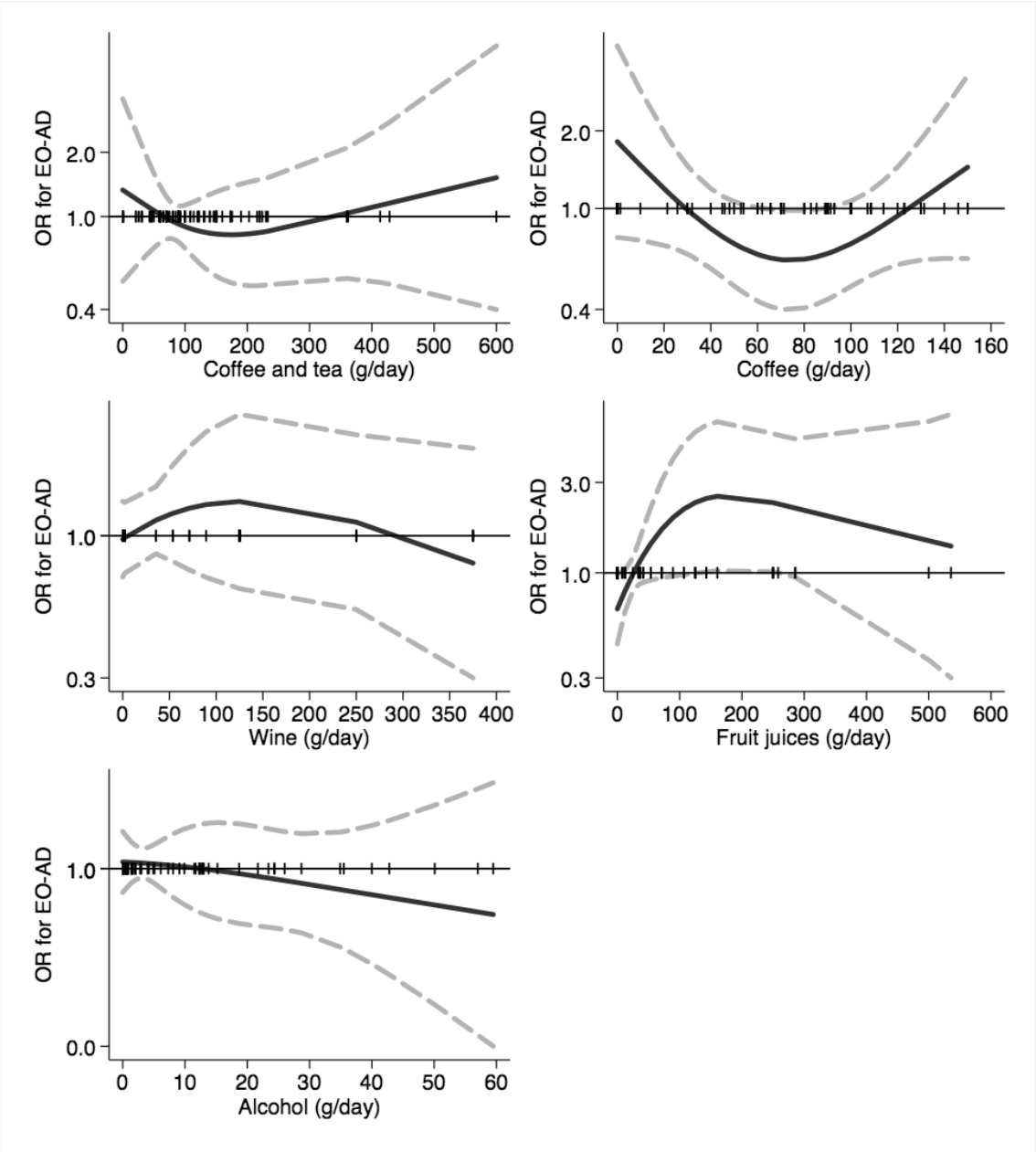


Figure 31. *Spline regression analysis of early onset Alzheimer's dementia (EO-AD) risk for increasing intake of food: beverages. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake. Note: spline analysis was not possible for offal and most of beverages due to few subjects reporting consumption different from a null value (tea, red, white and aperitif wines and beers, spirits and soft drinks).*

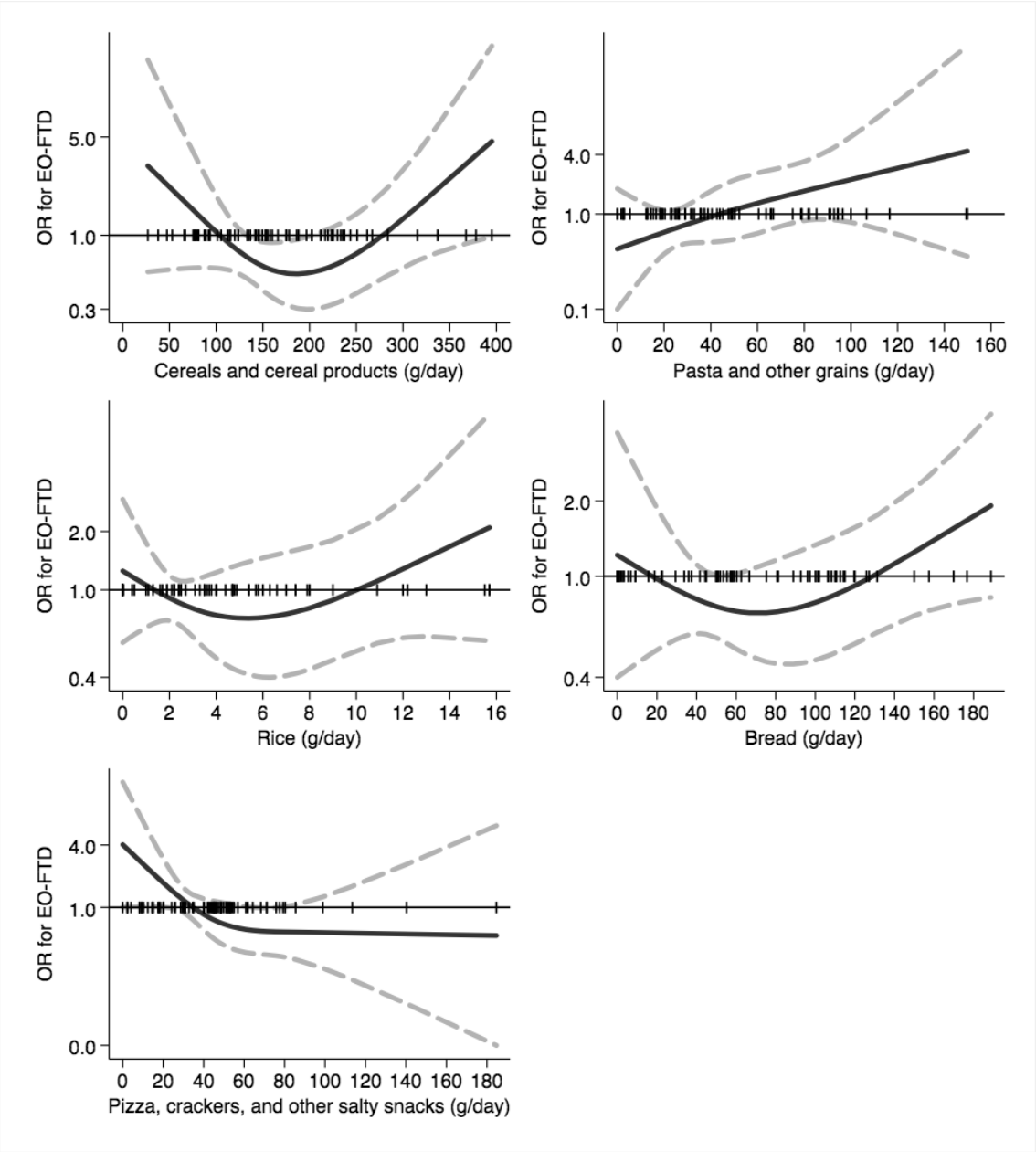


Figure 32. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: cereals and cereal products. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

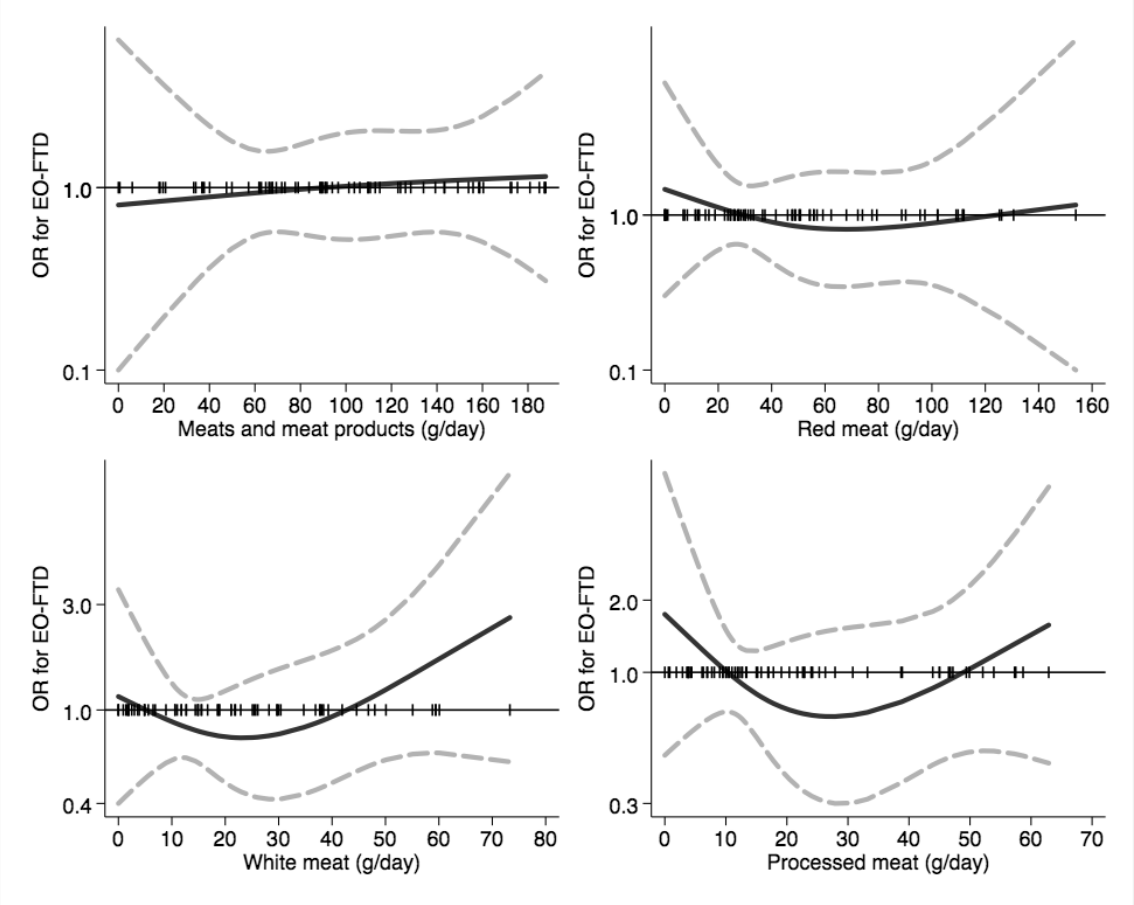


Figure 33. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: meats and meat products. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

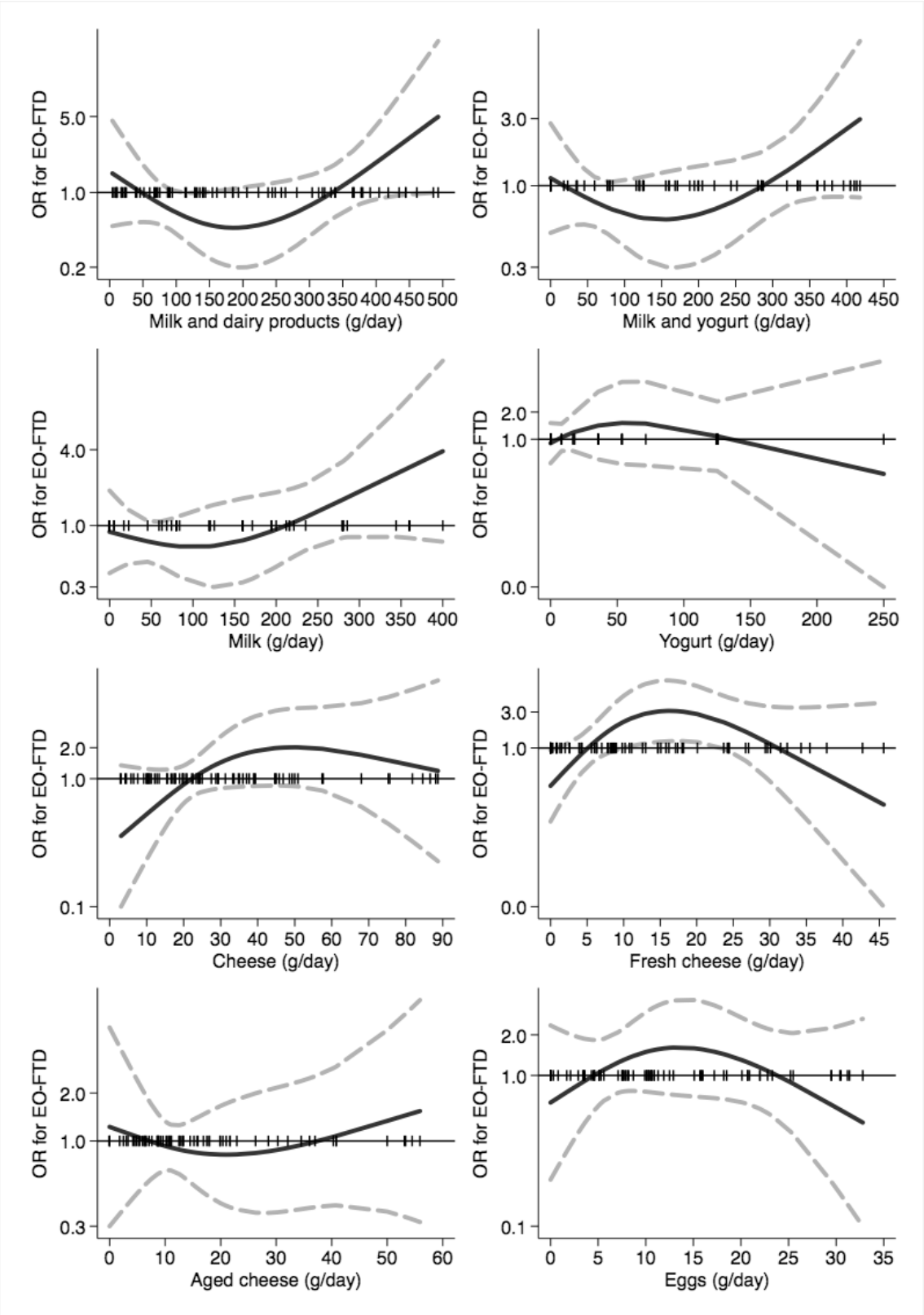


Figure 34. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: dairy products and eggs. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

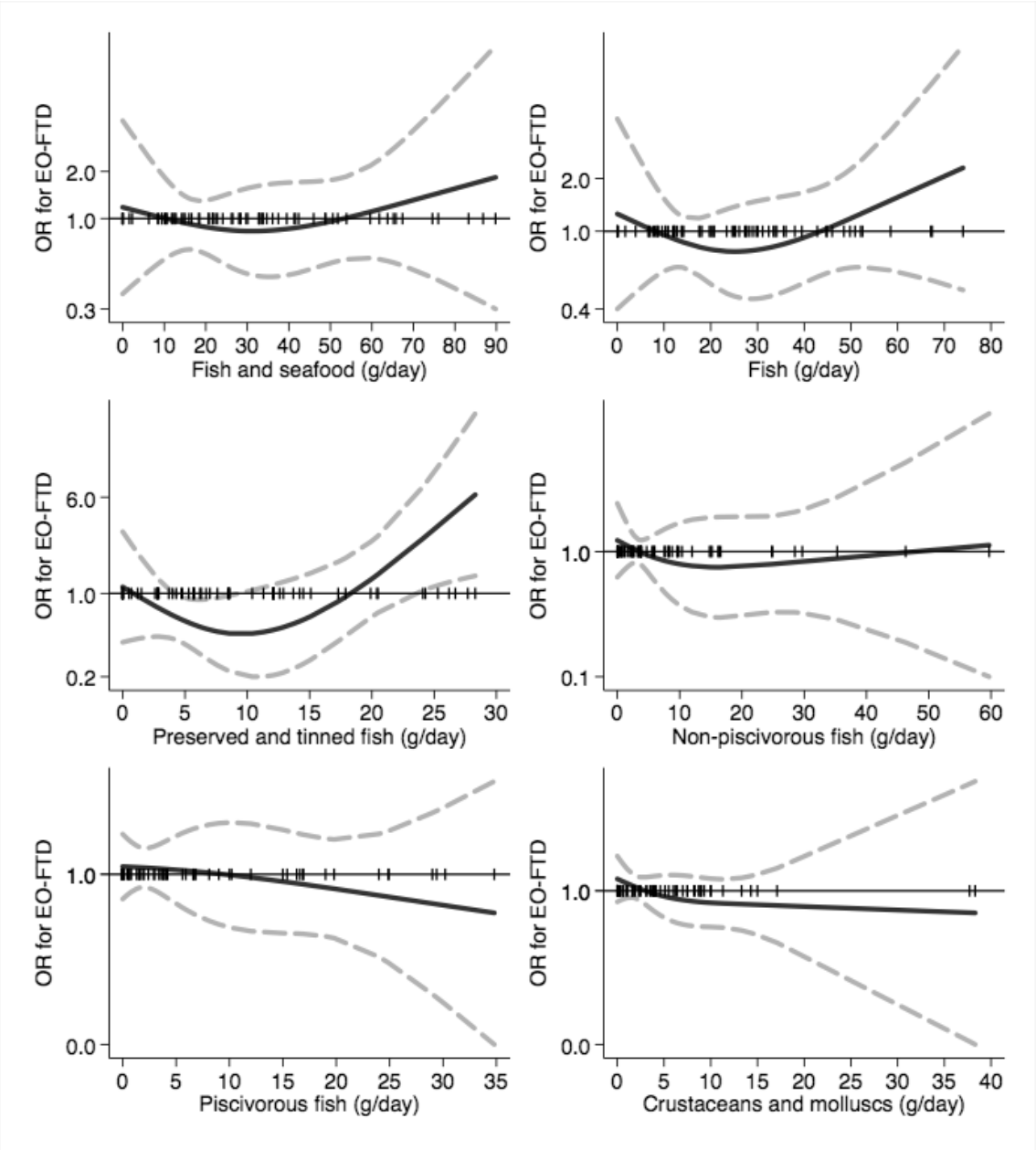


Figure 35. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: fish and seafood. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

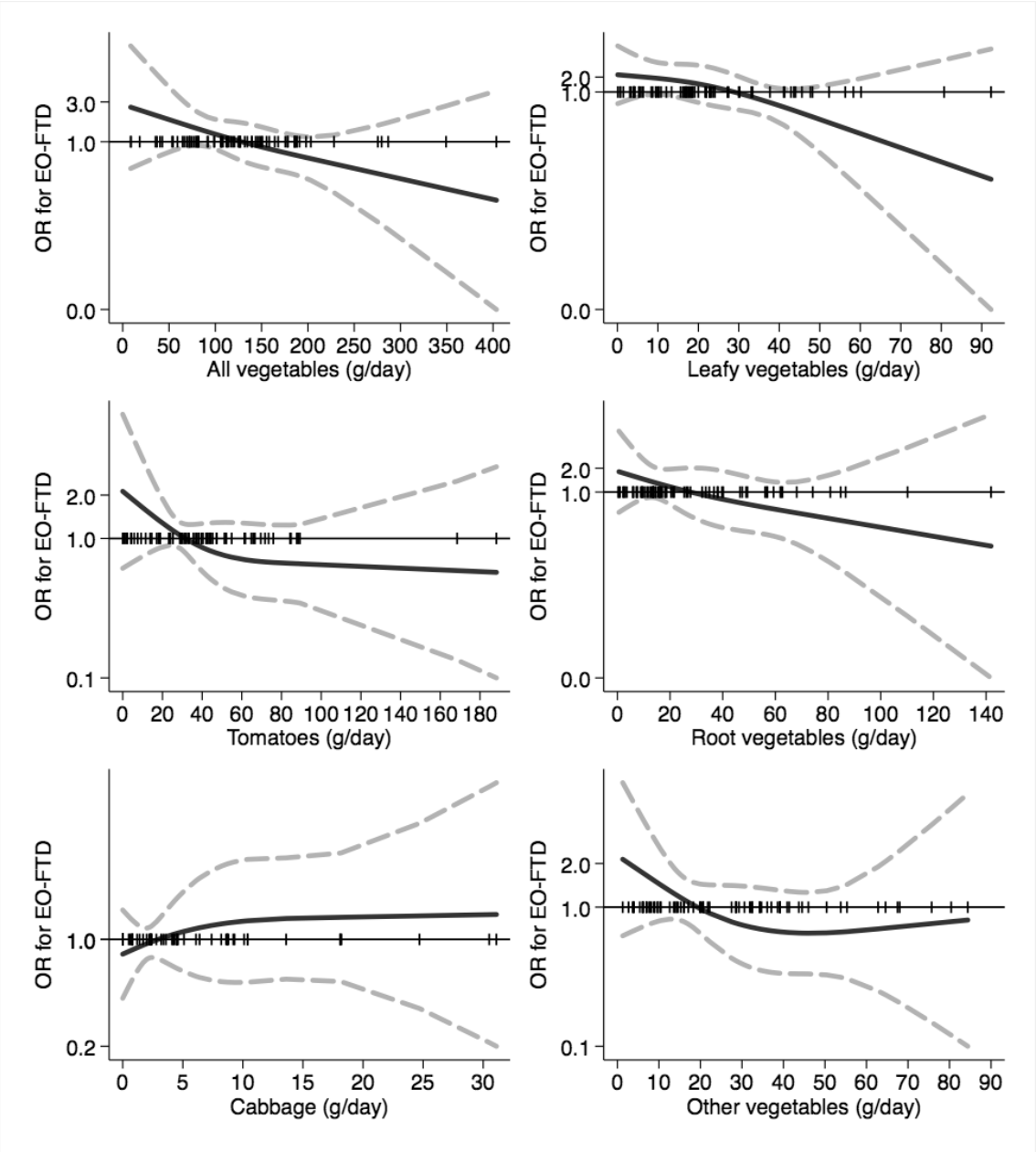


Figure 36. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: vegetables. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

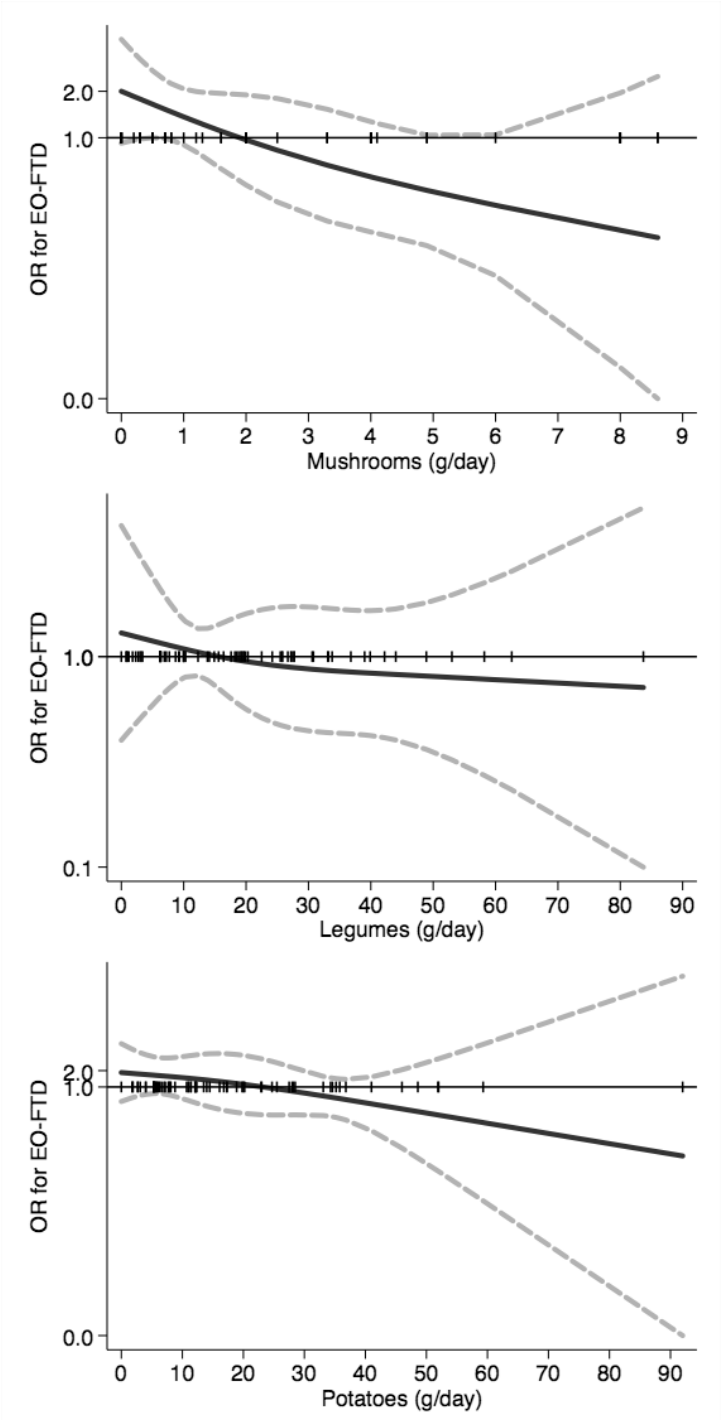


Figure 37. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: mushrooms, legumes and potatoes. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

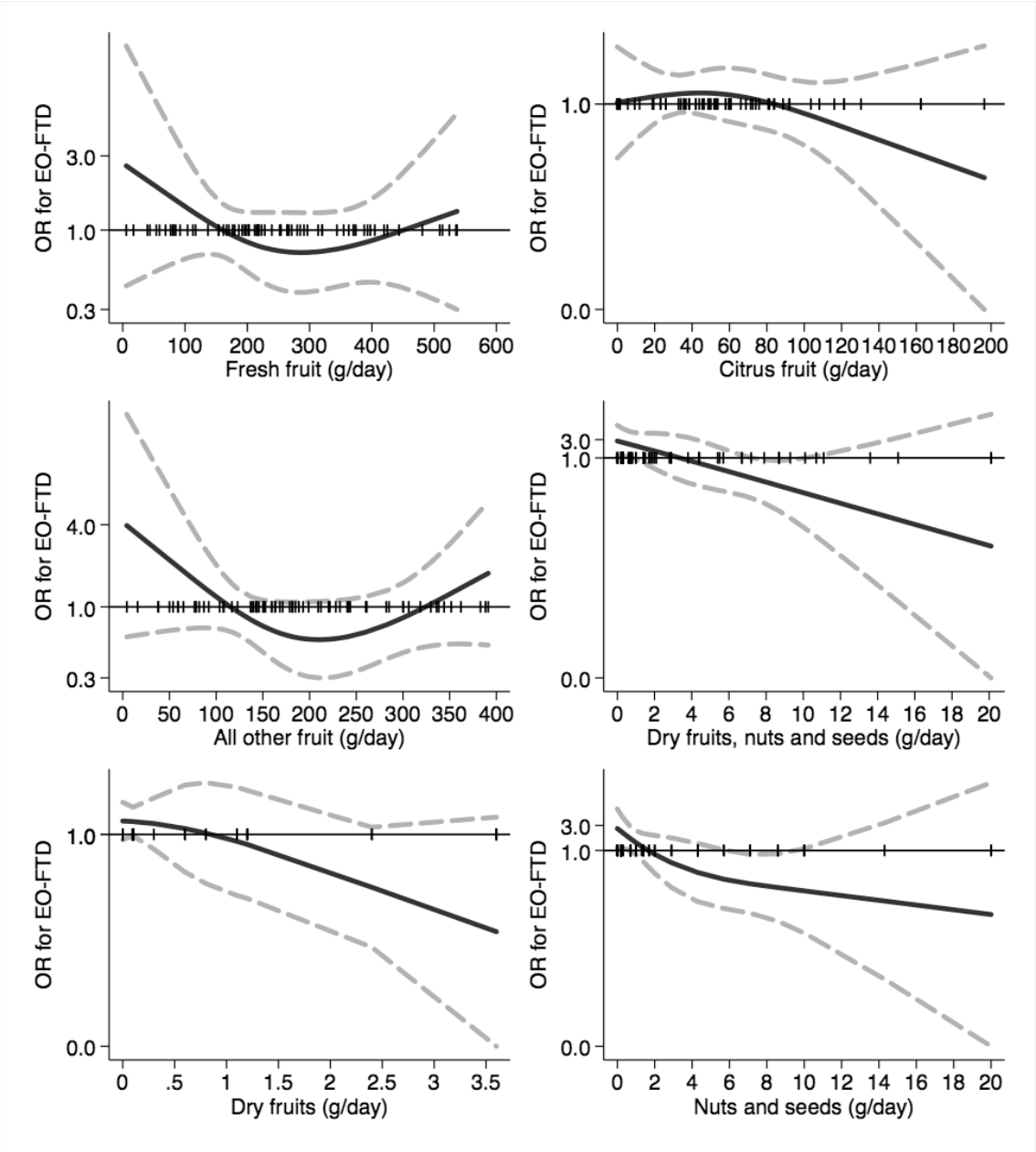


Figure 38. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: fresh and dry fruits. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

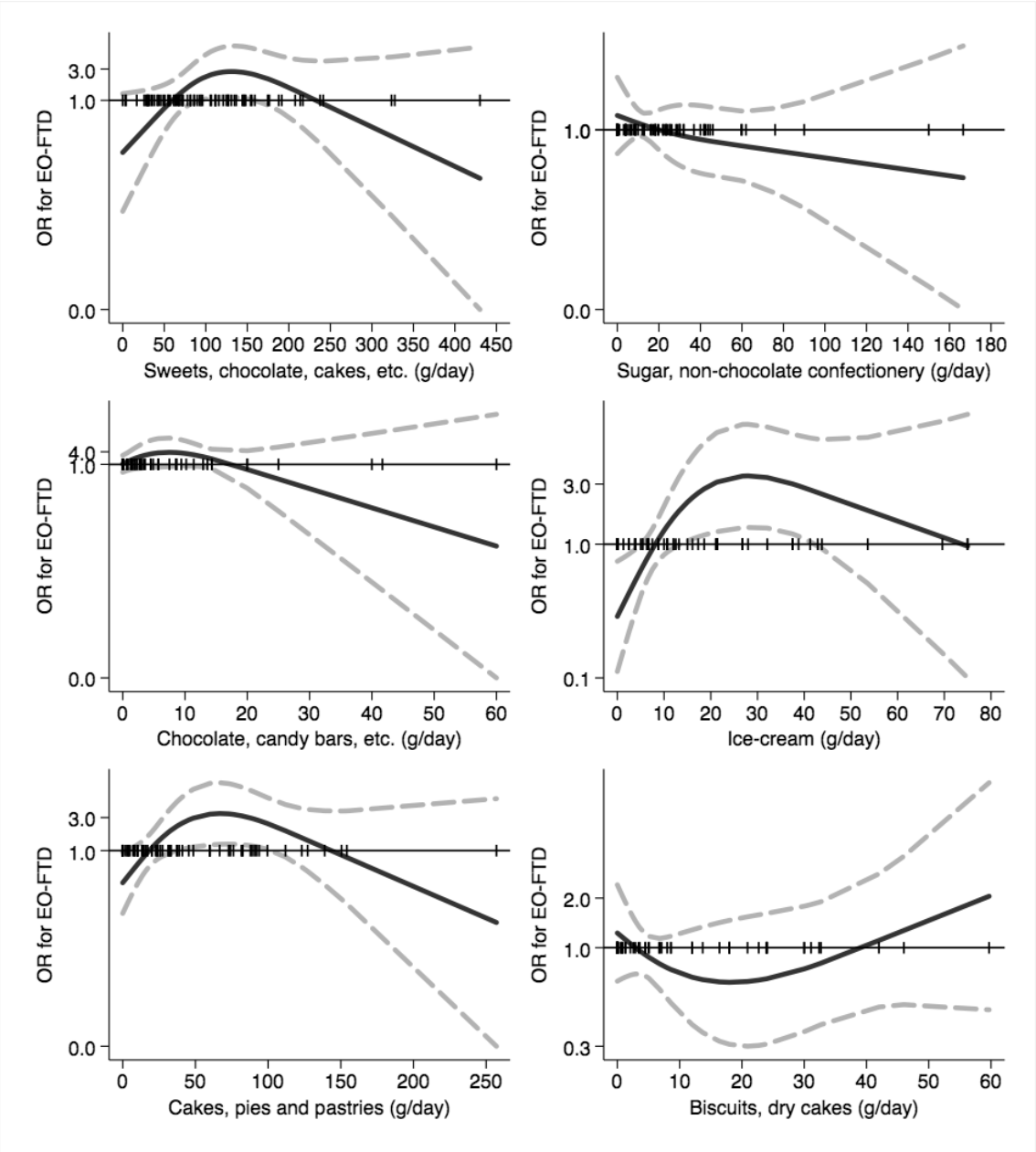


Figure 39. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: sweets, chocolate, cakes, etc. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

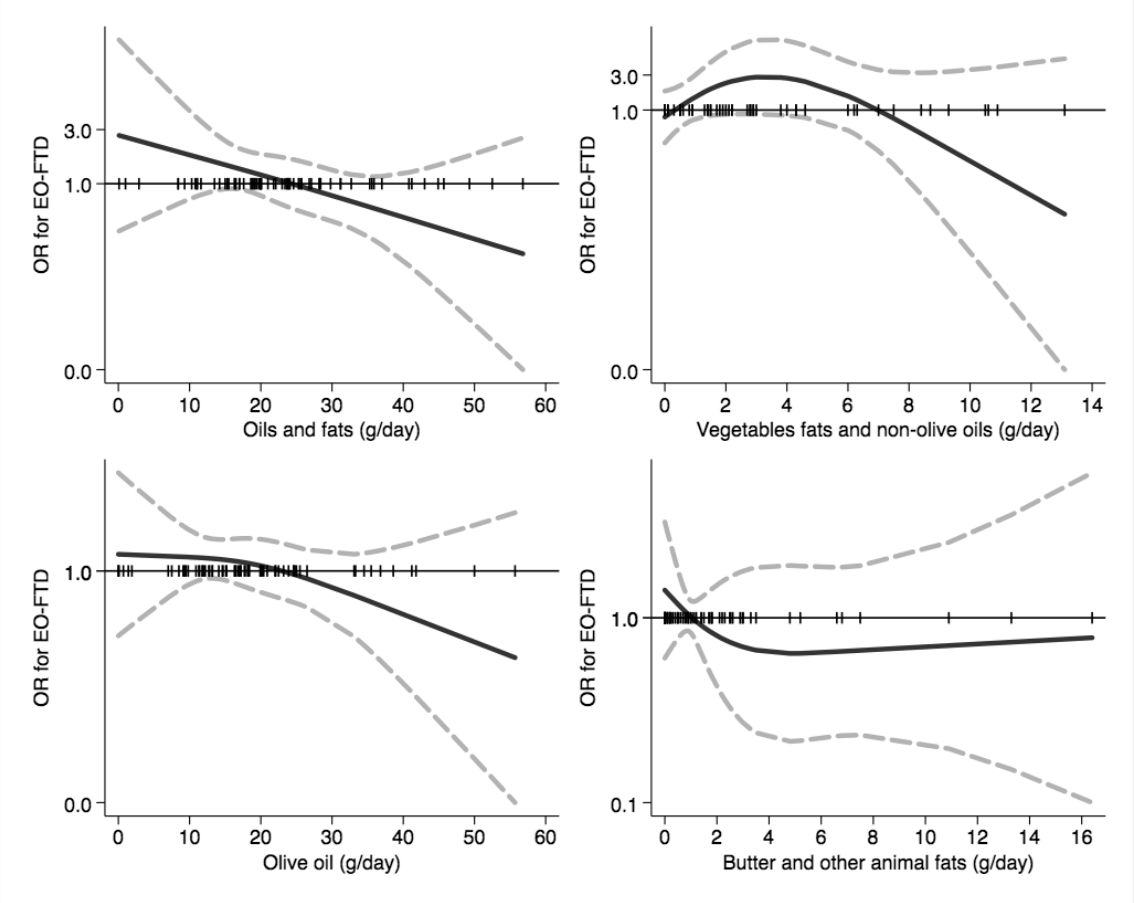


Figure 40. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: oils and fats. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake.*

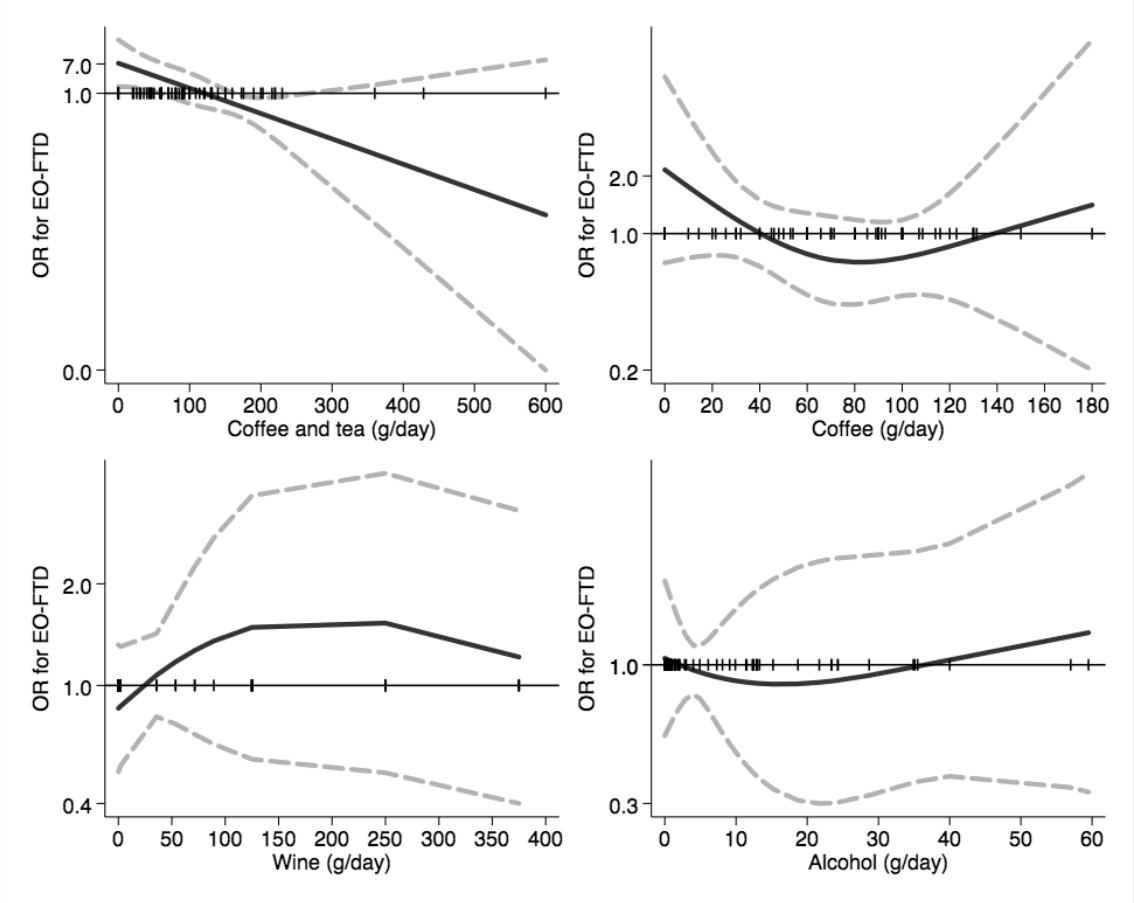


Figure 41. *Spline regression analysis of early onset frontotemporal dementia spectrum (EO-FTD) risk for increasing intake of food: beverages. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with black spikes indicates the distribution of participant intake. Note: spline analysis was not possible for offal and most of beverages due to few subjects reporting consumption different from a null value (tea, red, white and aperitif wines and beers, spirits and soft drinks).*

Spline regression analysis carried out for dietary pattern adherence showed no substantial association between EOD risk and both GM and DASH diets, with a reduction in risk from a score of ≥6 and ≥28, respectively (**Figure 42**). Conversely, a substantially linear inverse association emerged for the MIND diet, with higher risk at very low adherence and decreasing risk above a total score around 8/9. We found comparable results in the analyses performed by EOD subtype (**Figure 43** and **Figure 44**), with the exception of adherence to the DASH diet. This dietary pattern showed an inverse U-shaped relation with EO-FTD risk, with decreased risk for subjects at very low and very high adherence levels (**Figure 44**), while no association emerged for EO-AD (**Figure 43**).

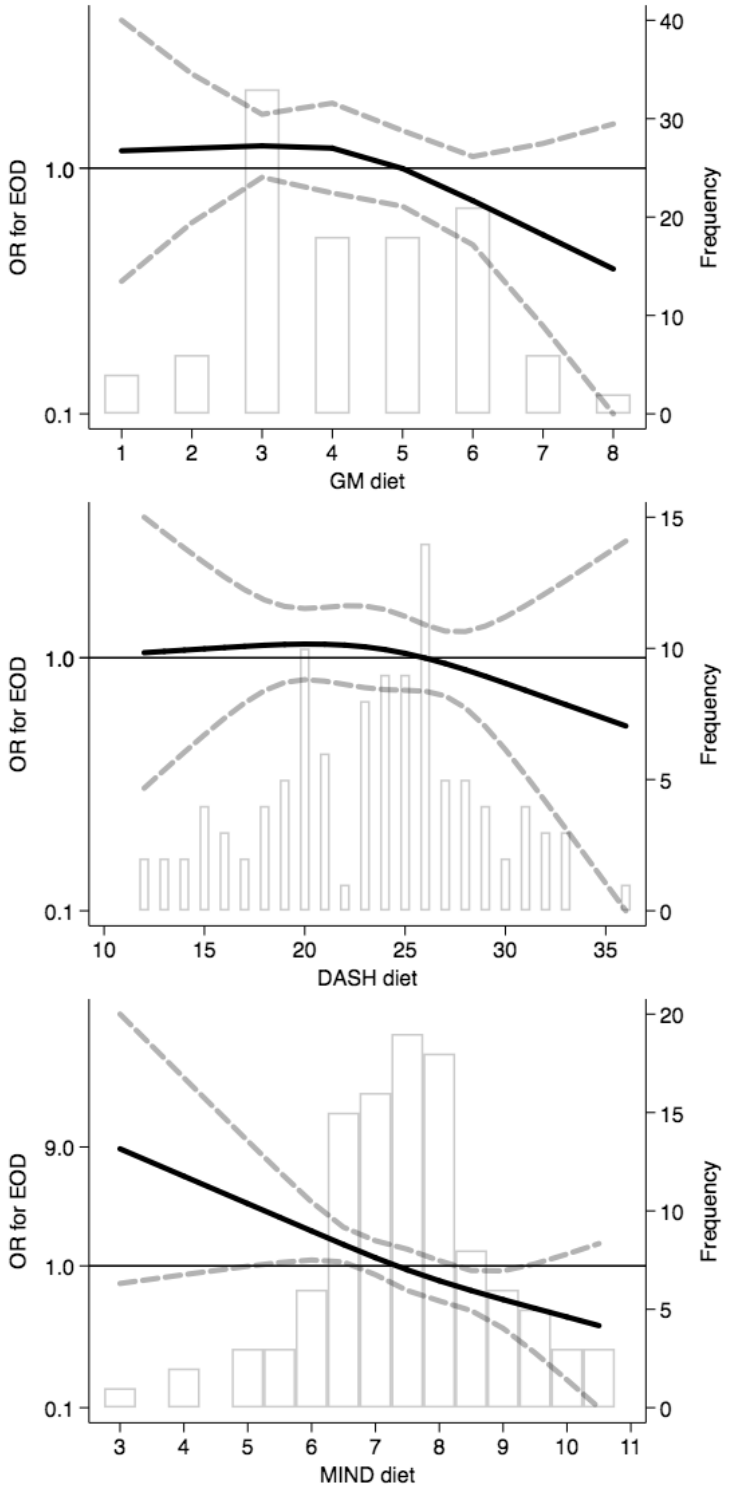


Figure 42. *Spline regression analysis for dietary patterns. Greek-Mediterranean (GM) diet, Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. The black line indicates odds ratios for dementia risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with gray bars shows dietary-pattern score distribution.*

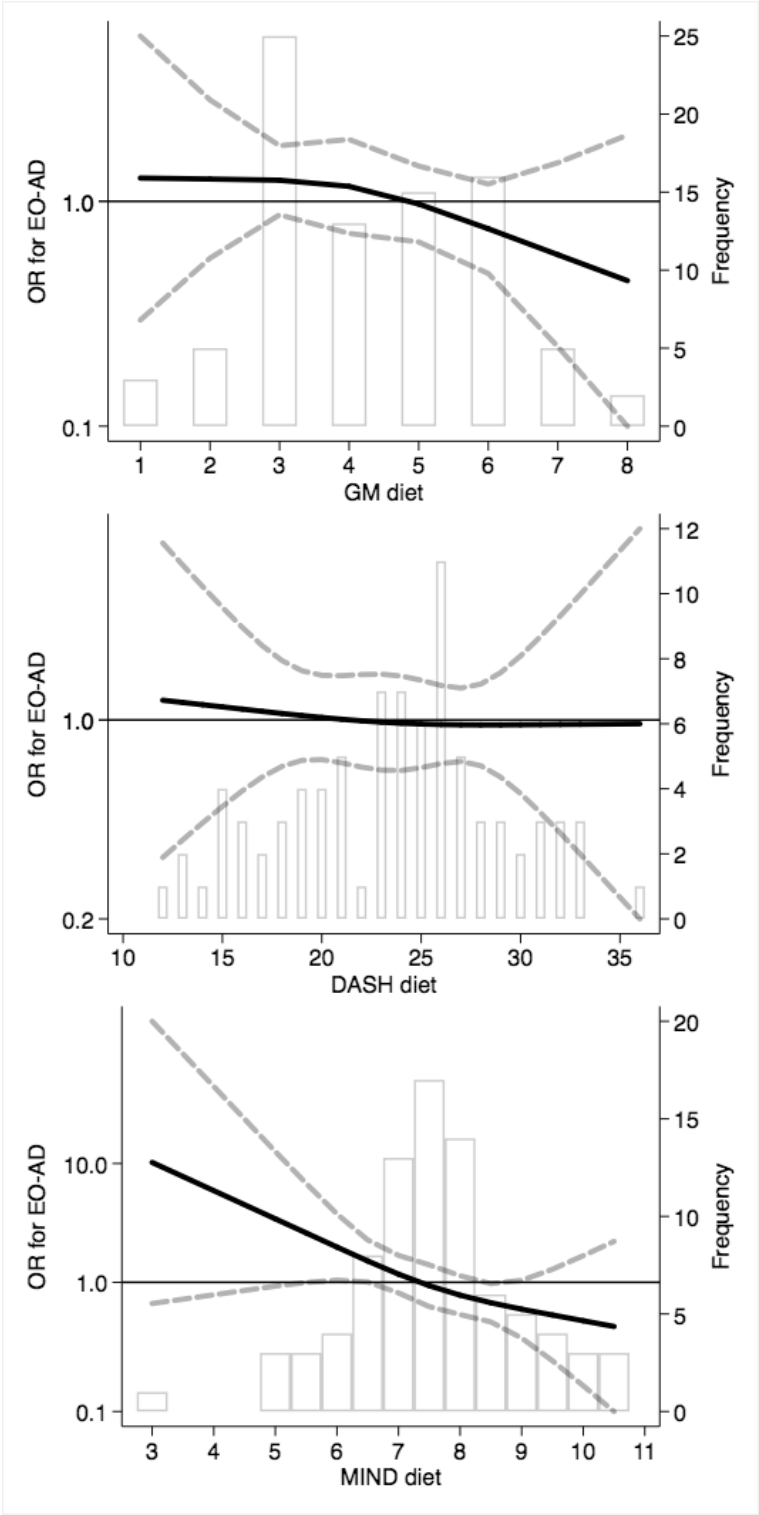


Figure 43. *Spline regression analysis for dietary patterns. Greek-Mediterranean (GM) diet, Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. The black line indicates odds ratios for early onset Alzheimer's dementia (EO-AD) risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with gray bars shows dietary-pattern score distribution.*

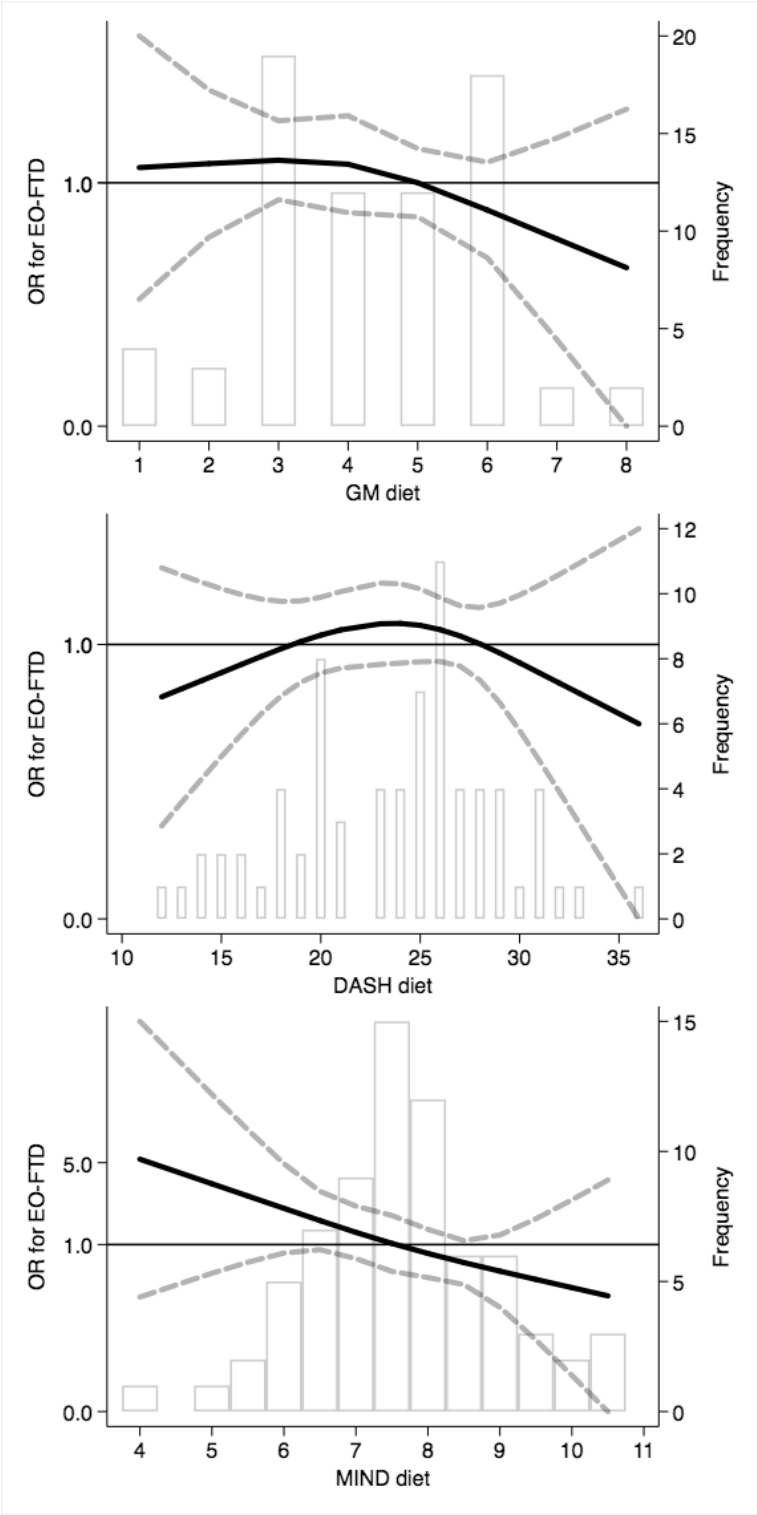


Figure 44. *Spline regression analysis for dietary patterns. Greek-Mediterranean (GM) diet, Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. The black line indicates odds ratios for frontotemporal dementia spectrum (EO-FTD) risk; dash gray lines are 95% confidence limits; the reference line at 1.0 with gray bars shows dietary-pattern score distribution.*

Discussion

In this study, we investigated a wide spectrum of potential environmental risk factors of EOD, including exposure to outdoor LAN, some of which had not been previously assessed with reference to disease etiology, to the best of our knowledge. In our assessment, we included putative risk factors based on their neurotoxicity shown by laboratory studies, and on their association with risk of late onset Alzheimer's dementia. In addition, we evaluated the role of dietary factors and patterns based on the assessment of dietary habits through administration of a validated FFQ. Moreover, we selectively investigated the association of these risk factors with the two most common early onset dementias, namely EO-FTD and EO-AD, hypothesizing a different etiology for these two diseases. This was a distinctive feature of our study compared with previous epidemiologic investigations.

Lifestyle, environmental occupational risk factors

We found evidence of a beneficial role of educational attainment for EOD prevention, consistent with what has been suggested for late onset dementia [122]. Our results are consistent with those of a Dutch study [123], while no such association emerged in a Swedish study [71].

In our study, widow status appeared to be a risk factor for EOD. This appears to be in keeping with previous findings reporting a higher risk of developing dementia, in both early and late onset forms, and for subjects widowed, divorced or single [124, 125], with increased likelihood for middle-aged individuals [124]. In our study, being single was less related to the development of dementia than being widowed. This could be linked to the psychological consequence of remaining alone after a couple life, compared with never having had a stable partner. In fact, stress could impact oxidative and neurotrophic factor signalling acting on the plasticity of neural networks and favoring the mechanisms underpinning Alzheimer's dementia [126, 127].

We found an indication that history of upper arm and head trauma requiring medical evaluation may be a risk factor for EOD, albeit in differential ways depending on dementia diagnosis. In particular, upper arm trauma was associated with increased EO-AD risk, while head trauma was associated with EO-FTD risk. This last finding is consistent with previous studies: a case-control study on 80 FTD subjects compared to 124 controls reported an OR of 3.3 (95% CI 1.3–8.1) for head trauma [128]. Moreover, a case-control study on war veterans found an association between traumatic brain injuries and dementia in FTD patients, which was stronger than in patients affected by other dementia types [129]. These results were confirmed by a recent review reporting a higher prevalence of traumatic brain injuries in FTD patients than in other dementia forms [130]. The possible underlying mechanism could depend on the induction of oxidative stress and microglial activation by trauma [131, 132]. Studies on chronic traumatic encephalopathy, a progressive tauopathy occurring in sport players exposed to mild traumatic brain injuries such as concussions,

for instance in America football, provide further evidence of the role of head trauma as a risk factor for dementia [133].

Concerning sports practice, we found an increased EOD risk in football (soccer) players. Such excess risk was much higher for EO-FTD than for EO-AD, and up to twice as high in professional players compared with non-competitive ones. Such excess risk may be due to the increased risk of head trauma characterizing that sport [134]. The increased risk linked to cycling similarly seemed to be only related to EO-FTD cases, in contrast with previous studies suggesting a protective effect of cycling on global cognition [135]. Conversely, we found evidence of beneficial effects of sports in general for both EO-AD and EO-FTD cases. This appears to be the case particularly for swimming, even if only in association with EO-AD cases. Sports practice might have a beneficial effect on late onset dementia according to systematic reviews [136-138] and meta-analyses [139, 140], while the association of EOD was only investigated in relation to traumatic sports [141, 142]. There is some biological plausibility for a beneficial effect of sports on dementia risk, linked to positive effects on insulin and C-peptide metabolism, as recently demonstrated in subjects with a family history of diabetes [143]. Impaired glycaemia and insulin resistance may predict brain amyloid deposition in late middle-aged adults as well as progressive cognitive impairment [144, 145], and their reduction could therefore be beneficial against dementia etiopathogenesis.

We observed a slightly increased EOD risk associated with herbicide and fungicide use during gardening. Such excess risk was much higher for EO-FTD compared with EO-AD. These associations were strengthened when considering occupational exposure to chemicals including fertilizers, pesticides and other substances. Our findings are consistent with previous studies evaluating the possible association between pesticides and late onset dementia, recently summarized in a meta-analysis which yielded a relative risk of 1.5 (95% CI 1.0–2.3) for AD at all ages [146]. Nevertheless, null results about this association in late onset dementia have also been reported, at least for organochlorine pesticides [147].

Very few studies have assessed the role of occupational exposure to solvents and dyes, as well as refrigerants or degreasing agents, in EOD etiology [148-151]. In our study, we found an increased risk associated with occupational exposure to aluminum, although based on an extremely low number of cases and therefore statistically very imprecise. Even though there is some biological plausibility for such association [152], a study in Northern England assessing aluminum exposure through drinking water found no association with Alzheimer's dementia, although the levels involved were much lower than potentially toxic ones [153]. Conversely, an increased risk of Alzheimer's dementia was found to be associated with aluminum exposure both during occupational exposure and through drinking water [154]. In our study, nevertheless, the association found for overall EOD was mostly driven by excess exposure in EO-FTD. This could be explained by the hypothesis of a common disease spectrum of this type of dementia with motor neuron disease, namely amyotrophic

lateral sclerosis (ALS), a disease whose etiology may involve most of the risk factors we found to be associated with EO-FTD [155]. In particular, some forms of FTD and ALS share the pathological substrate, the transactive DNA-binding protein 43 (TDP-43) and the C9ORF72 gene [155, 156], as well as some environmental risk factors including agricultural chemicals, professional sports involving high risk of mild traumatic brain injuries such as concussion and subconcussion [133], leading to a pro-oxidative state and consequent neuron degeneration and astrocyte dysfunction [106, 157, 158].

In our study, long-term use of selenium-containing dietary supplements was associated with a considerably increased risk, only partially mitigated after excluding specific "neuroprotective" supplements taken after disease onset to reduce the risk of reverse causation. If we consider only EO-FTD patients, however, results were of even stronger relevance, thus reducing the risk of bias of reverse causality. While there is clear evidence that vitamin and mineral self-supplementation do not prevent cognitive decline or dementia [159, 160], the possibility that some constituents of dietary supplements, namely selenium, may exert deleterious effects on cognition should also be considered, taking into account previous results in humans and the related biological plausibility [161, 162].

Finally, our results seem to confirm that smoking, already found to be associated with dementia risk in some studies [163] and particularly in apolipoprotein E ε4 non-carriers [164], may be a risk factor for EOD. However, the relation between smoking and dementia has not been confirmed by some recent studies on overall dementia risk [165, 166] and a meta-analysis on EOD based on three studies [70].

Light at night

As regards exposure to outdoor light at night (LAN), artificial lighting is widespread and increasingly worldwide, especially in developed countries. Given the high exposure to light at night for most of the population, it is important to study its impact on health. Some effects caused by lighting exposure during night hours on humans are now well known, first of all the alteration of the circadian rhythm, the worsening of sleep quality and the reduction of melatonin production depending on the wavelength and intensity of light [85, 167-169]. This is due to the fact that the night lighting affect brain functioning at the level of the suprachiasmatic nucleus, the so-called biological human clock, influenced by the alternation of phases of light and dark. In fact, light is believed to be the most powerful regulator of the circadian rhythm. The synthesis of melatonin in the pineal gland generally occurs at night in the absence of light, not only during the hours of sleep. Therefore, having artificially prolonged the hours of light, the population is moving towards a general lack of melatonin. Both experimental studies on animal models and human epidemiological studies have shown an

association between the dysregulation of the circadian rhythm and the nocturnal inhibition of melatonin synthesis with tumor pathologies [167, 169]

Exposure to LAN induces insomnia and sleep disturbances which can contribute to the onset of chronic diseases. Furthermore, it appears that it may also act as a stressor at the level of the immune system [169]. Night lighting has been correlated not only with cancer, but also with aging, cardiovascular disease, diabetes, behavioral disorders, obesity, and neurodegenerative diseases [169].

The mechanisms through which LAN can affect brain functions have been studied and investigated in animal models. A study conducted on rodents (Swiss albino mice) evaluated consecutive exposure for three weeks to a light with an intensity of 5 lux. The results showed how exposure to LAN leads to alteration of cognitive and non-cognitive behavior. At the cellular level, an increase in oxidative stress was observed with lipid peroxidation, a reduction in the activity of the superoxide dismutase enzyme and catalase, both enzymes with antioxidant action. While at the hippocampal level, a reduction in the levels of brain-derived neurotrophic factor, synapsin II and doublecortin (DCX) was observed. Furthermore, an inhibition of CREB and SIRT1 mRNA production was observed. Finally, pyramidal and cortical neurons exhibited chromatolysis and a pycnotic appearance [170].

For the study of Alzheimer's dementia, a *Drosophila melanogaster* animal model characterized by expression of human phosphorylated tau protein exposed to light at nigh showed the ability to accumulate such protein leading to apoptosis in neurons [89]. This first experimental study showed how even low light pollution can affect the circadian rhythm and the sleep-wake rhythm. In a second study carried out on *Drosophila melanogaster* animal model, the mechanism underlying the correlation between circadian rhythm and neurodegeneration was investigated [171]: several proteins were identified to correlate with the alterations in the circadian rhythm, induced in this experiment through prolonged exposure to light during the night, with a reduced elimination of the tau protein and consequent toxicity. Indeed, there appears to be a correlation between factors that regulate the circadian rhythm, pathways of cell death and toxicity induced by the accumulation of tau protein with the remodeling of neurons in the optic lobe of *Drosophila* [171].

Dietary habits

The role of dietary habits on cognitive decline has been investigated in previous studies [172], but the real association between diet and dementia, along with the mechanisms involved in beneficial and detrimental effects, are still unclear and thoroughly debated. In addition, it should be noted that previous studies were generally performed among individuals with late onset dementia, while the present study specifically focused on younger subjects. Consistent with previous findings, we found a protective effect on EOD particularly with higher consumption of leafy vegetables and fresh fruit.

This protective effect on cognitive decline could be linked to the consumption of foods rich in bioactive substances such as polyphenols, highly present in fruits, vegetables, cereals, coffee/tea, cacao and wine [173-175]. In the studies suggesting that vegetable intake showed an inverse association with cognitive decline [176, 177], an apparent beneficial role of consumption of leafy and root vegetables has been reported [178, 179]. Conversely, fruit intake showed contrasting results with null [177, 179] or inverse association [175], with the latter mainly emerging from the analysis evaluating dry fruit intake [173, 179, 180].

Similarly, intake of omega-3 fatty acids due to fish consumption has been linked to improved cognition capacities [174, 176, 181-184]. Interestingly, we found null association when overall fish and seafood intake was considered, whereas a slight decrease in risk could be found when considering fish, particularly fresh fish, only. The association we detected between a high daily intake of preserved and tinned fish and EOD is of interest, since such intake in Italy is mainly due to consumption of canned tuna [185], a source of heavy metals such as mercury, lead, cadmium and a metalloid of potential neurotoxicity such as selenium [161, 185-189].

Contrasting results with detrimental [190, 191] or null effects [112, 192] have been reported for dairy products. However, a preventive role has not yet been entirely ruled out, especially considering the different types of dairy products [193, 194]. In particular, we found a dose-dependent association between dairy products and EOD risk. In addition, a null to negative association was observed for subjects reporting an intake of up to 350 g/day, when EOD risk starts to increase, thus suggesting adverse effects only at very high intake levels. A possible beneficial role in cognitive function of substances released during fermentation processes, such as oleamide and dehydroergosterol, has been suggested, following suppression of microglial inflammation as well as promotion of synaptic extension and neuronal survival [195].

High cereal intake seems associated with sharper cognitive decline [191]. In our study, we found an optimum cereal intake at approximately 200 g/day with reference to EOD risk. This is not surprising in that cereals (particularly bread) are fundamental components of the Mediterranean diet [93]. This mainly relates to a beneficial effect of whole grain consumption [196], possibly due to high concentrations of dietary fiber, resistant starch and oligosaccharides as well as several phytochemicals (phytates and phenolic compounds) characterized by antioxidant activities [197].

Sweets are generally associated with adverse cognitive effects [198, 199]. Possible biological mechanisms of that association may involve generally high fat contents, especially high in saturated and trans-fats and lower in polyunsaturated and monounsaturated fats leading to blood brain barrier dysfunction and increased amyloid beta protein aggregation [200]. However, we observed an indication of beneficial effects from moderate consumption of chocolate products, consistent with previous studies [201, 202]. Such beneficial effects, if real, may be due to cocoa polyphenol intake [203] that might slower MCI progression to dementia [204].

We found a clear inverse association between coffee consumption and EOD risk. A recent dose-response meta-analysis of prospective studies [205] showed a statistically imprecise U-shaped relation between coffee intake and all-cause dementia risk, with the lowest dementia risk at 2 cups/day (RR=0.90, 95% CI 0.95 to 1.08) and increased risk at and above 5 cups/day (RR=1.11, 95% CI 0.94 to 1.30). Estimate imprecision might be due to the heterogeneity of exposure assessment methods (i.e. cups), which may correspond to different coffee amounts depending on country. Nonetheless, we also found a U-shaped association with lowest risk at 70 g/day, corresponding to approximately two small (i.e. 'espresso type') cups, according to typically Italian habits as assessed in the EPIC-FFQ [206, 207]. Contrary to our expectations based on the epidemiologic literature, we found find no clear and meaningful relation between wine or alcohol intake and disease risk. No consumption and excessive consumption of wine or alcohol have both been associated with increased dementia risk [208, 209]. In particular, a J-shaped relation has been proposed where low-to-moderate intake was associated with reduced risk, while both null and elevated intakes were correlated with increased risk [210-212].

Concerning dietary patterns, our results for EOD are fully consistent with previous studies, although these were generally carried out in older individuals, suggesting a beneficial effect on overall cognitive function at higher adherence levels [102, 114, 213-218]. In particular, we found an indication of protective effects on EOD risk only at high adherence levels to the Greek-Mediterranean Diet (≥6) and DASH index (≥28). On the other hand, the only diet that was strongly and linearly associated with EOD risk was the MIND pattern. This was not entirely unexpected, since the MIND pattern has been shown to better predict incidence of cognitive impairment or cognitive decline as compared to the Mediterranean Diet and DASH index [219, 220]. In addition, the MIND diet has shown beneficial effects on other neurological diseases [119-121], while a clinical trial about the role of diet on cognitive decline and brain neurodegeneration is ongoing [221].

The three dietary patterns under investigation have some similarities, because they emphasize natural plant-based foods and limit the intake of animal-derived products and high saturated-fats. Nevertheless, MIND has a distinctive pattern. It was developed as a hybrid of the DASH and Mediterranean diets with modifications, by reflecting most compelling scientific evidence on foods and nutrients that protect the brain [222]. The MIND pattern attributes beneficial effects to the intake of cheese (<1 serving/week), green leafy vegetables (≥ 6 servings/week), berries (>1 serving/week), and fast fried food (< 1 time/week) [102, 215]. In addition, high adherence to the investigated dietary patterns is generally associated with high levels of physical activity and other diet-related lifestyle factors [93] having beneficial effects on cognitive function [223, 224]. These factors were not taken into account in our study. They might have contributed to lower EOD risk and to masking the effect of the diet, which becomes evident only at high adherence levels.

Limitations and strengths

We acknowledge some limitations of our study. First, the number of cases and controls was limited, and the number of exposed subjects was very low for many of the environmental factors we investigated. This increased the statistical imprecision of the risk estimates and clearly hampered our ability to reliably identify 'slight' causal associations. Moreover, we could not exclude the occurrence of some selection bias, linked to the case-control nature of the study. This could be true to some extent for controls (caregivers), while it is less likely for cases, since we tried to include all subjects referred in the study period to the two Cognitive Neurology clinics, the only ones providing specialized clinical care to EOD patients for the whole territory of the province. Therefore, it is unlikely that EOD patients from the underlying population of the province could not have been referred to these clinics. Since the study was based on self-completed questionnaires and on long-term exposure, we also cannot entirely rule out some degree of recall bias. However, environmental risk factors for EOD are poorly recognized and even perceived not to exist in the general population, thus making the occurrence of such bias rather unlikely.

Another limitation linked to the observational nature of the study consists in the possible presence of residual confounding not evaluated. In particular for LAN exposure, the role of atmospheric pollution, a probable risk factor for dementia and AD in particular [69, 225] cannot be evaluated, though a positive association with light pollution has been suggested [85].

Furthermore, the use of caregivers as controls could have led to some mitigation of the real association between environmental risk factors and disease risk in our study, because most of the caregivers were family members and may have shared lifestyle habits with EOD cases, thus reducing the strength of the associations we estimated. Finally, we have no availability of genetic status for the referent population, thus precluding the possibility of assessing their role in disease risk [226, 227].

With reference to the strengths of this study, we included recently-diagnosed EOD cases, thus limiting the risk of bias related to a long duration of the disease due to disease progression and increasing disability. Another strength of the present study was the ability to apply stratified analyses for several lifestyles, environmental, occupational factors and also dietary habits with EOD risk also according to the main clinical dementia types, namely EO-AD and EO-FTD, pointing out possible different etiological mechanisms. In addition to the best of our knowledge, this study is the first to investigate the role of dietary factors on early onset dementia risk. In fact, previous studies focused on late onset dementia or did not implement specific restriction to EOD cases. The use of the validated EPIC-FFQ also allowed for a comprehensive assessment of dietary habits, including the investigation of single food categories and overall dietary-pattern adherence. Finally about LAN assessment, the use of a GIS (Geographic Information System) allowed to carry out an objective evaluation of the extent of exposure to LAN not based on a self-assessment of the subjects.

Conclusions

In this case-control study in a Northern Italy population, we identified positive associations between EOD and environmental factors such as occupational exposure to aluminum, pesticides and other chemicals (dyes, paints or thinners), long-term use of selenium-containing dietary supplements, as well as smoking and playing football, while overall sports practice appeared to be a strong protective factor for EOD. Some of these potential etiologic factors showed different associations with disease risk when the two most common EOD forms were independently considered. Also LAN exposure might increase risk of EOD, especially Alzheimer's dementia with early onset. Finally, this study provides insights on the role of dietary factors in EOD risk. In particular, our findings suggest a detrimental effect on EOD risk due to high intake of cereals, dairy products, and some types of sweets. Conversely, intake of some types of fish, vegetables, dry fruits and chocolate alongside moderate coffee consumption appear to be beneficial. Finally, our study indicates that increasing adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) may decrease EOD risk.

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Appendix 1. Study questionnaire

Lifestyle, environmental and occupational questionnaire

Scheda di rilevazione dati per il Progetto EOD

La ringraziamo per la collaborazione a questa ricerca sui fattori di rischio delle Early Onset Dementia che prevede l'auto-compilazione dei seguenti questionari.
Il suo contributo sarà per noi molto prezioso per approfondire e ricercare le cause alla base di tali patologie.

Il questionario è suddiviso in otto sezioni:

A) Informazioni personali

B) Informazioni cliniche

C) Informazioni sulla storia occupazionale

D) Informazioni sugli hobbies o altre attività

E) Informazioni sulla storia residenziale

F) Informazioni sull'utilizzo residenziale di pesticidi

G) Informazioni su aspetti odontoiatrici e generali

H) Riservato alle donne

Cognome Nome	_____/_____	**Data di compilazione**	____ / ____ / ____ *gg* *mm* *aa*

Compilazione a cura del personale medico			
Codice ID	|__|__|__|__|	**Numero progressivo**	|__|__|__|__|

Sezione A - Informazioni personali

ID:

A.1 Sesso 1) F 2) M **A.2 Data di nascita** (gg|mm|aa) |___|___|___|

A.3 Dove è nato/a?

Comune |_____| Provincia |_____| Nazione |_____|

A.4 Quanto pesa(kg)? |__|__|__| **A.5. Quanto è alto/a (m)** |__|,|__|__|

A.6 Quante persone siete in famiglia (incluso/a lei)? |__|__|

A.7 Attualmente con chi vive?

1) Solo/a
2) Con il coniuge/convivente
3) Coabitazione familiare (figli, fratelli/sorelle, genitori, altri parenti)
4) Coabitazione non familiare (amici, congregazione, istituto)

A.8 Attualmente, lei è:

1) Coniugato **(passare alla domanda A.11)**
2) Convivente **(passare alla domanda A.11)**
3) Single **(passare alla domanda A.11)**
4) Religioso/a (prete, suora, ecc) **(passare alla domanda A.11)**
5) Separato/divorziato **(passare alla domanda A.9)**
6) Vedovo/a **(passare alla domanda A.10)**

A.9 In che anno si è separato/o ha divorziato da suo marito/moglie? |__|__|__|__|

A.10 In quale data il suo coniuge è deceduto/a? (gg|mm|aa) |___|___|___|

A10.1 Qual è stata la causa del decesso del suo coniuge? |_____|

A.11 Ha perso un figlio?

1) SI (proseguire con la domanda A.11.1)
2) NO (passare alla domanda A.12)

A.11.1 In quale data suo figlio è deceduto/a? (gg|mm|aa) |___|___|___|

A.11.1 Qual è stata la causa del decesso di suo figlio? |_____|

A.12 Qual è il più alto titolo di studio che ha conseguito?

1) Nessun titolo
2) Licenza elementare
3) Licenza media
4) Diploma superiore
5) Laurea

A.13 Ha svolto il servizio militare?

1) SI (proseguire con la domanda A.13.1)

2) NO (passare alla domanda A.13.2)

A.13.1. Se No, perché |_____|

A.13.2 In quale anno? |__|__|__|__|

A.13.3 Dove? Città |_____| Provincia |___|

A.13.4 Che ruolo ricopriva? |_____|

Sezione B - Informazioni cliniche

B.1 In quale data è stata fatta la diagnosi della malattia? (gg|mm|aa) |___|___|___|

B.2 In quale struttura sanitaria le è stata fatta la diagnosi? |_____|

B.3 Ha mai subito dei traumatismi che abbiano avuto bisogno di valutazione medica?

	Sede	Risposta		Quante volte?	Età ultimo traumatismo
a)	Testa	1) SI	2) NO	|__|__|__|	|__|__|__|
b)	Tronco	1) SI	2) NO	|__|__|__|	|__|__|__|
c)	Braccio destro	1) SI	2) NO	|__|__|__|	|__|__|__|
d)	Braccio sinistro	1) SI	2) NO	|__|__|__|	|__|__|__|
e)	Gamba destra	1) SI	2) NO	|__|__|__|	|__|__|__|
f)	Gamba sinistra	1) SI	2) NO	|__|__|__|	|__|__|__|

B.4 Hai mai subito shock elettrici? 1) SI 2) NO

B.5 Se sì, in quale anno? |__|__|__|__|

B.6 Ha subito interventi chirurgici? 1) SI 2) NO (passare alla domanda B.7)

B.6.1 Se sì, quali e a che età (anni)?

_____	|__|__|	_____	|__|__|
_____	|__|__|	_____	|__|__|
_____	|__|__|	_____	|__|__|

B.7 E' mai stato sottoposto ad anestesia generale? 1) SI 2) NO (passare alla domanda B.8)

B.7.2 Se sì, quali (locale, epidurale, generale, ecc) e a che età?

_____	|____|	_____	|____|
_____	|____|	_____	|____|
_____	|____|	_____	|____|

Anamnesi patologica

B.8 Le è mai stata fatta diagnosi di?

1)	Ipertensione arteriosa	1) SI	2) NO
2)	Fibrillazione atriale	1) SI	2) NO
3)	Infarto del miocardio/angina	1) SI	2) NO
4)	Ictus	1) SI	2) NO
5)	Placche ai vasi del collo	1) SI	2) NO
6)	Bronchite cronica o enfisema	1) SI	2) NO
7)	Malattie infiammatorie intestinali (Morbo di Crohn, Rettocolite ulcerosa)	1) SI	2) NO
8)	Celiachia	1) SI	2) NO
9)	Epatite cronica o cirrosi	1) SI	2) NO
10)	Malattie della tiroide o noduli tiroidei	1) SI	2) NO
11)	Diabete	1) SI	2) NO
12)	Dislipidemia (colesterolo e/o trigliceridi alti)	1) SI	2) NO
13)	Ansia o depressione o psicosi	1) SI	2) NO
14)	Malattia di Parkinson	1) SI	2) NO
15)	LES (lupus eritematoso sistemico)	1) SI	2) NO
16)	Malattie delle valvole cardiache	1) SI	2) NO
17)	Tumori	1) SI	2) NO
18)	Sindrome di Down	1) SI	2) NO

Anamnesi familiare

B.9 Qualcuno dei suoi familiari ha sofferto di una o più delle seguenti patologie?

		Madre	**Padre**	**Fratelli/Sorelle**	**Altri consanguinei** (nonni, zii e cugini di I grado)
a)	Demenza	1)	2)	3)	4)
b)	Parkinson	1)	2)	3)	4)
c)	Ictus	1)	2)	3)	4)
d)	Infarto cardiaco	1)	2)	3)	4)
e)	Ipertensione arteriosa	1)	2)	3)	4)
f)	Diabete	1)	2)	3)	4)
g)	Colesterolo e/o trigliceridi alti	1)	2)	3)	4)

h)	Depressione	1)	2)	3)	4)
i)	Alzheimer	1)	2)	3)	4)
j)	Psicosi	1)	2)	3)	4)
k)	Alcolismo	1)	2)	3)	4)
l)	Ritardo mentale	1)	2)	3)	4)
m)	Sindrome di Down	1)	2)	3)	4)

B.10 I suoi genitori sono ancora viventi? 1) SI (passare alla domanda C.1) 2) NO

Se no:

B.11 A che età è morto suo padre? |__|__| Per quale motivo? _____

B.12 A che età è morta sua madre? |__|__| Per quale motivo? _____

B.13 Ha dei conoscenti con la sua stessa patologia?

1) SI (proseguire con la domanda B.13.1)
2) NO (passare alla sezione C)

B.13.1 Specificare i conoscenti con la sua stessa patologia:

1) vicini di casa
2) colleghi di lavoro
3) amici del circolo sportivo
4) altro (specificare) _____

Sezione C - Informazioni sulla storia occupazionale

C.1 Qual è la sua condizione lavorativa attuale?

1) Lavoratore a tempo pieno
2) Lavoratore part-time
3) Pensionato
4) Casalinga
5) Studente
6) Disoccupato
7) Altro (specificare)_____

C.2 In quale dei seguenti settori ha prevalentemente svolto la sua attività lavorativa?
(indicare una sola risposta)

1) Agricoltura, caccia, pesca
2) Industria, estrazione, manifatture, energia
3) Costruzioni
4) Commercio (ingrosso e dettaglio), alberghi e ristoranti

5) Trasporti, magazzinaggio e comunicazioni

6) Intermediazioni, noleggio

7) Pubblica amministrazione e difesa

8) Istruzione, sanità ed altri servizi sociali

9) Altri settori (specificare)_____

C.3 Quale attività lavorativa sta svolgendo e quali ha svolto in precedenza per almeno 1 anno?

N	Ditta (nome e indirizzo)	Datore di lavoro (nome intestatario)	Settore	Mansione	Anno di inizio	Anno di fine
a)						
b)						
c)						
d)						
e)						
f)						
g)						

C.4 Ora, leggerà una lista di agenti chimici e fisici ai quali potrebbe essere stato esposto durante il suo lavoro o qualunque attività lavorativa da lei svolta. Sono soltanto alcuni esempi di sostanze che potrebbero essere state inalate o con le quali si è venuti a contatto mediante la pelle.

Durante il suo lavoro, è venuto a contatto con:

	Sostanza	**Risposta**		**In quale anno?**	**Per quanti anni?**
a)	Piombo in ogni sua forma (fumi, polveri, particelle)	1) SI	2) NO	|__|__|__|__|	|__|__|__|
b)	Mercurio in ogni sua forma (fumi, polveri, particelle)	1) SI	2) NO	|__|__|__|__|	|__|__|__|
c)	Selenio	1) SI	2) NO	|__|__|__|__|	|__|__|__|
d)	Cadmio	1) SI	2) NO	|__|__|__|__|	|__|__|__|
e)	Arsenico	1) SI	2) NO	|__|__|__|__|	|__|__|__|
f)	Alluminio	1) SI	2) NO	|__|__|__|__|	|__|__|__|
g)	Insetticidi	1) SI	2) NO	|__|__|__|__|	|__|__|__|
h)	Erbicidi	1) SI	2) NO	|__|__|__|__|	|__|__|__|
i)	Fungicidi	1) SI	2) NO	|__|__|__|__|	|__|__|__|
j)	Pitture ad olio	1) SI	2) NO	|__|__|__|__|	|__|__|__|

k)	Diluenti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
l)	Svernicianti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
m)	Vernici	1) SI	2) NO	|__|__|__|__|	|__|__|__|
n)	Adesivi	1) SI	2) NO	|__|__|__|__|	|__|__|__|
o)	Coloranti o inchiostri da stampa	1) SI	2) NO	|__|__|__|__|	|__|__|__|
p)	Oli lubrificanti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
q)	Antigelo e refrigeranti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
r)	Sgrassanti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
s)	Solventi, come toluene o xilene	1) SI	2) NO	|__|__|__|__|	|__|__|__|
t)	Prodotti per la pulizia a secco	1) SI	2) NO	|__|__|__|__|	|__|__|__|
u)	Gas anestetici	1) SI	2) NO	|__|__|__|__|	|__|__|__|
v)	Attrezzature macchinari elettrici ed elettronici	1) SI	2) NO	|__|__|__|__|	|__|__|__|
w)	Campi elettromagnetici	1) SI	2) NO	|__|__|__|__|	|__|__|__|
x)	Altro_____			|__|__|__|__|	|__|__|__|

C.5 Se ha lavorato nel settore agricolo in particolare, è stato a contatto con:

	Sostanza	**Risposta**		**In quale anno?**	**Per quanti anni?**
a)	Fertilizzanti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
b)	Pesticidi	1) SI	2) NO	|__|__|__|__|	|__|__|__|
c)	Disinfettanti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
d)	Detergenti	1) SI	2) NO	|__|__|__|__|	|__|__|__|
e)	Solventi	1) SI	2) NO	|__|__|__|__|	|__|__|__|
f)	Olii per macchine agricole	1) SI	2) NO	|__|__|__|__|	|__|__|__|
g)	Gasoli/benzine per mezzi ed attrezzature agricole	1) SI	2) NO	|__|__|__|__|	|__|__|__|
h)	Altro_____	1) SI	2) NO	|__|__|__|__|	|__|__|__|

C.6 In particolare, se ha utilizzato pesticidi, compili, per quanto possibile, la tabella sottostante:

Denominazione commerciale	Tipo di prodotto (es. erbicida)	Composizione (sostanza attiva e concentrazione)	In quale anno?	Per quanti anni?
a)				
b)				
c)				

C.7 Durante la sua attività lavorativa ha svolto mansioni che prevedevano l'utilizzo dei seguenti dispositivi di protezione individuale? Se sì, specifichi la frequenza dell'utilizzo:

	Dispositivo			**Tutto il tempo**	**Spesso**	**Mai**	**Non so**
a)	Guanti, come neoprene o nitrile	1) SI	2) NO	1)	2)	3)	4)
b)	Maschera a filtro antipolvere	1) SI	2) NO	1)	2)	3)	4)
c)	Maschera antigas	1) SI	2) NO	1)	2)	3)	4)
d)	Grembiule, tuta o abbigliamento esterno removibile	1) SI	2) NO	1)	2)	3)	4)
e)	Altro_____			1)	2)	3)	4)

C.8 E' mai stato coinvolto in un incidente sul lavoro con versamento di grandi quantità di sostanze utilizzate? 1) SI 2) NO (passare alla domanda C.9)
Se sì,
C.8.1 Quale sostanza? (specificare) |_____|
C.8.2 Quante volte è successo? |__|__|

C.9 Ha mai avuto malessere o nausea per un'esposizione lavorativa?
1) SI 2) NO (passare alla domanda D.1)
Se sì,
C.9.1 A quale sostanza? (specificare) |_____|
C.9.2 Quante volte è successo? |__|__|

Sezione D - Informazioni sugli hobbies o altre attività al di fuori della Sua attività lavorativa

D.1 E' mai andato a caccia? 1) SI 2) NO (passare alla domanda D.2)
D.1.1.Quanti anni aveva quando ha iniziato? |__|__|
D.1.2 Per quanti anni ha svolto questo hobby? |__|__|

D.2 E' mai andato a pescare? 1) SI 2) NO (passare alla domanda D.3)
D.2.1. Quanti anni aveva quando ha iniziato? |__|__|
D.2.2. Per quanti anni ha svolto questo hobby? |__|__|
D.2.3. Utilizzava i piombi per svolgere questo hobby? 1) SI 2) NO

D.3 Ha mai dipinto? 1) SI 2) NO (passare alla domanda D.4)

D3.1 Quanti anni aveva quando ha iniziato? |__|__|

D3.2 Per quanti anni ha svolto questo hobby? |__|__|

D3.3 Per dipingere utilizzava vernici a base di olio? 1) SI 2) NO

D.4 Costruiva modellini usando la colla? 1) SI 2) NO (passare alla domanda D.5)

D4.1 Quanti anni aveva quando ha iniziato? |__|__|

D4.2 Per quanti anni ha svolto questo hobby? |__|__|

D.5 Ha mai fatto giardinaggio? 1) SI 2) NO (passare alla domanda D.6)

D5.1 Quanti anni aveva quando ha iniziato? |__|__|

D5.2 Per quanti anni ha svolto questa attività? |__|__|

D5.3 Durante tale attività utilizzava insetticidi? 1) SI 2) NO

D5.4 Durante tale attività utilizzava diserbanti? 1) SI 2) NO

D5.5 Durante tale attività utilizzava prodotti per le muffe o la ruggine?

1) SI 2) NO

D.6 Ha l'hobby per la fotografia? 1) SI 2) NO (passare alla domanda D.7)

D6.1 Quanti anni aveva quando ha iniziato? |__|__|

D6.2 Per quanti anni ha svolto questo hobby? |__|__|

D.7 Ha praticato dello sport? 1) SI 2) NO (passare alla domanda D.8)

D.7.1 Quali sport ha praticato nella sua vita?

Sport	**A che età ha iniziato?**	**Per quanti anni?**	**Per quante ore alla settimana?**	**Specificare il livello: agonistico / non agonistico**	
a)				☐	☐
b)				☐	☐
c)				☐	☐
d)				☐	☐
e)				☐	☐
f)				☐	☐

D.8 Troverà qui di seguito un elenco di alcuni prodotti (integratori vitaminici e alimentari, cosmetici, farmaci ecc) contenenti SELENIO. Segni quelli che assume/ha assunto o utilizza/ha utilizzato negli ultimi 20 anni, specificando la frequenza di utilizzo:

	Prodotto/integratore		Quantità di: BUSTINE, COMPRESSE o CAPSULE assunte al giorno	Assunto per qualche: giorno	settima	mese	anno
1)	Acqua termale di LaRoche Posay	☐		☐	☐	☐	☐
2)	AcutilMultivitaminico Plus e Senior	☐		☐	☐	☐	☐
3)	Adrusen Crono	☐		☐	☐	☐	☐
4)	Anasten Plus	☐		☐	☐	☐	☐
5)	Andrositol Buste	☐		☐	☐	☐	☐
6)	Angstrom Intensive Tan (Melanin Complex)	☐		☐	☐	☐	☐
7)	Argivit	☐		☐	☐	☐	☐
8)	Artrosulfur compresse	☐		☐	☐	☐	☐
9)	Balance plus Multiminerale	☐		☐	☐	☐	☐
10)	Betaeffe Plus	☐		☐	☐	☐	☐
11)	Bioesse Plus	☐		☐	☐	☐	☐
12)	Biokap miglio (integratore capelli unghie)	☐		☐	☐	☐	☐
13)	Biokromaton Mineral Vit EF	☐		☐	☐	☐	☐
14)	Biomineral One e Biomineral Plus	☐		☐	☐	☐	☐
15)	BioNike Defence Age	☐		☐	☐	☐	☐
16)	BioNike Defence Sun	☐		☐	☐	☐	☐
17)	Bios Line centri pura	☐		☐	☐	☐	☐
18)	Bioscalin Antiforfora	☐		☐	☐	☐	☐
19)	Bioscalin unghie	☐		☐	☐	☐	☐
20)	Cromovit Integratore dietetico	☐		☐	☐	☐	☐
21)	Dercos shampoo	☐		☐	☐	☐	☐
22)	Enervit protein 6 barrette	☐		☐	☐	☐	☐

23)	Estro+ integratore fitoestrogeni	☐		☐	☐	☐	☐
24)	Evestrel giorno-notte (integratore menopausa)	☐		☐	☐	☐	☐
25)	Exfoliac Femme Perfection	☐		☐	☐	☐	☐
26)	Ferti Plus integratore	☐		☐	☐	☐	☐
27)	Fortiflex 525 compresse	☐		☐	☐	☐	☐
28)	Galenia Flebion 400	☐		☐	☐	☐	☐
29)	Gestalys DHA (per gestanti)	☐		☐	☐	☐	☐
30)	GojiSan succo puro	☐		☐	☐	☐	☐
31)	Gynefam plus	☐		☐	☐	☐	☐
32)	Hydreane legere crema pelle	☐		☐	☐	☐	☐
33)	Immugen e Immugen R	☐		☐	☐	☐	☐
34)	Inneov pre-Hyaluron	☐		☐	☐	☐	☐
35)	Integra Antiossidante (Bioflavonoidi + Selenio + Vitamine ACE)	☐		☐	☐	☐	☐
36)	Kerium shampoo	☐		☐	☐	☐	☐
37)	Lichtena Norma-ACN integratore	☐		☐	☐	☐	☐
38)	Lierac Solaire Bronzage capsules	☐		☐	☐	☐	☐
39)	Lierac sunif preparateur capsules	☐		☐	☐	☐	☐
40)	Lievitovit (capelli) e Lievitovit (Depurante)	☐		☐	☐	☐	☐
41)	Lutegenol	☐		☐	☐	☐	☐
42)	Macular Active	☐		☐	☐	☐	☐
43)	Megavir	☐		☐	☐	☐	☐
44)	MgK Vis Ricarica Plus	☐		☐	☐	☐	☐
45)	Migliocres capelli	☐		☐	☐	☐	☐
46)	Mithen	☐		☐	☐	☐	☐
47)	Multicentrum (Baby, Junior, Select 50+)	☐		☐	☐	☐	☐
48)	Neobros C	☐		☐	☐	☐	☐

49)	Neovis (Plus e Tres)	☐		☐	☐	☐	☐
50)	Nolder	☐		☐	☐	☐	☐
51)	Normon UV-free capsule	☐		☐	☐	☐	☐
52)	Nutrof total	☐		☐	☐	☐	☐
53)	Ocuclar F	☐		☐	☐	☐	☐
54)	Ocustress c/estratto di eleuterococco	☐		☐	☐	☐	☐
55)	Oenobiol Antiage	☐		☐	☐	☐	☐
56)	Oenobiol Solaire Duo	☐		☐	☐	☐	☐
57)	Officina pelle biorepair plus	☐		☐	☐	☐	☐
58)	Pesoforma barrette e Intensive crema	☐		☐	☐	☐	☐
59)	Pharcos triconicon (integratore alimentare)	☐		☐	☐	☐	☐
60)	Phytobronz perle innovative formula	☐		☐	☐	☐	☐
61)	Revidox+ integratore duo	☐		☐	☐	☐	☐
62)	Rougj Caps	☐		☐	☐	☐	☐
63)	Selenium ACE Extra	☐		☐	☐	☐	☐
64)	Selsun blu	☐		☐	☐	☐	☐
65)	Selsun Blu Shampoo	☐		☐	☐	☐	☐
66)	Supradyn Vital age 50+	☐		☐	☐	☐	☐
67)	Tanning generator Complex	☐		☐	☐	☐	☐
68)	Taurovit	☐		☐	☐	☐	☐
69)	Tricoren (integratore nutrizionale donna)	☐		☐	☐	☐	☐
70)	Vita Sohn junior	☐		☐	☐	☐	☐
71)	Vitalmix mente	☐		☐	☐	☐	☐
72)	Vivi free pasta	☐		☐	☐	☐	☐
73)	Ymea silhouette	☐		☐	☐	☐	☐
74)	Altro _____	☐		☐	☐	☐	☐

D.9.1 Consuma abitualmente patate al selenio? 1) SI 2) NO

D.10 Ha mai fumato almeno una sigaretta al giorno almeno per 6 mesi?

1) SI 2) NO (passare alla domanda D.11)

D.10.1 Quanti anni aveva quando ha iniziato a fumare regolarmente? |__|__|

D.10.2 Quante sigarette in media ha fumato al giorno? |__|__|

D.10.3 Attualmente fuma? 1) SI 2) NO

D.10.4 Se no, quanti anni aveva quando ha smesso di fumare definitivamente? |__|__|

D.11 È esposto al fumo passivo di altre persone?

1) SI 2) NO (passare alla domanda E.1)

D.11.1 Per quanti giorni, in media, alla settimana? |__| giorni

D.11.2 Per quante ore, in media, al giorno? |__|__| ore/die

Sezione E: Informazioni sulla sua residenza

E.1 Ricostruisca la sua storia residenziale (residenza anagrafica o domicilio) dalla sua nascita ad oggi (compresa l'attuale) per soggiorni di ALMENO UN ANNO:

N	Periodo dal (anno)	Periodo al (anno)	Via, n°	Comune	Provincia	Nazione
a)						
b)						
c)						
d)						
e)						
f)						

Specificare tra le residenze precedenti:

E.2 Avete mai vissuto in una fattoria/azienda agricola/casa di campagna? 1) SI 2) NO

E.3 Qual è la vostra fonte primaria di acqua potabile?

1) Rete idrica comunale |__|__|__| %
2) Pozzo, cisterne, fontana o sorgente |__|__|__| %
3) Acqua in bottiglia |__|__|__| %
4) Altro (specificare) _____

E.4 Beve o ha mai bevuto acqua di pozzo privato, cisterna, fontana o sorgente?

1) SI 2) NO (passare alla domanda E.5)

E.4.1 Se SI, in quali anni? Dal |__|__|__|__| al |__|__|__|__|

e in che percentuale |__|__| %?

E.4.2 Può dirci a che profondità si trova il pozzo privato/cisterna/fontana o sorgente?

|__|__|m

E.5 Utilizza acqua di pozzo privato, cisterne, fontana o sorgente per la coltivazione di prodotti agricolo a consumo privato?

1) SI 2) NO (passare alla domanda E.6)

E.5.1 Se SI, in quali anni? Dal |__|__|__|__| al |__|__|__|__|

E.6 Può dirci a che profondità si trova il pozzo privato/cisterna/fontana o sorgente? |____|m

E.7 Ha mai vissuto in un luogo in cui fossero presenti a meno di 3 kilometri specchi d'acqua, acquitrini, pozzi, bacini, risaie, laghi, fiumi?

1) SI 2) NO (passare alla domanda E.8)

Se sì, può riportare qui di seguito l'indirizzo dell'abitazione (Via|Comune|Provincia)?

|_____|

E.8 Ha mai abitato in un luogo nelle cui vicinanze fossero presenti:

		Risposta	**Indirizzo**	**Distanza approssimativa (m)**
a)	Inceneritore	1) SI 2) NO	|__|__|__|__|	|__|__|__|__|
b)	Discariche	1) SI 2) NO	|__|__|__|__|	|__|__|__|__|
c)	Industrie	1) SI 2) NO	|__|__|__|__|	|__|__|__|__|
d)	Linee elettriche ad alta tensione	1) SI 2) NO	|__|__|__|__|	|__|__|__|__|

Sezione F: informazioni sul utilizzo residenziale di pesticidi

F.1 Utilizza pesticidi (diserbante, erbicida, insetticida, fungicida ecc.) per la sua abitazione?

1) SI (proseguire con la domanda F.2)

2) NO (passare alla domanda F.4)

Se sì:

	F.2 Per cosa utilizza i pesticidi?	**Con quale frequenza?**
a)	Per il prato e gli alberi esterni (es. per erbacce, malattie delle piante)	1) almeno 1 volta a settimana 2) almeno 1 volta all'anno
c)	Per le piante interne (per malattie delle piante, erbacce)	1) almeno 1 volta a settimana 2) almeno 1 volta all'anno
d)	Per gli insetti volanti (mosche, zanzare, api, vespe, calabroni o falene, altro)	1) almeno 1 volta a settimana 2) almeno 1 volta all'anno
e)	Per gli insetti striscianti (formiche, blatte, ragni, altro)	1) almeno 1 volta a settimana 2) almeno 1 volta all'anno
f)	Per i roditori (topi, ratti, scoiattoli, talpe, pipistrelli, altro)	1) almeno 1 volta a settimana 2) almeno 1 volta all'anno
g)	Per gli animali domestici (pulci, zecche, altro)	1) almeno 1 volta a settimana 2) almeno 1 volta all'anno
e)	Altro (specificare) _____	1) almeno 1 volta a settimana 2) almeno 1 volta all'anno

F.4 Sono mai stati fatti trattamenti massicci di disinfestazione in casa (si consideri sia l'interno che l'esterno)? 1) SI 2) NO (passare alla domanda F.5)

F.4.1 In quale residenza? _____

F.4.2 Verso quale parassita? _____

F4.3 Mi sa dire con quale sostanza? _____

F.4.4 Si ricorda quando?

1) Mentre vi abitava
2) Prima dell'occupazione
3) In entrambi i casi

F.5 Nei pressi della sua abitazione il Comune ha mai fatto spruzzare pesticidi per insetti (falene, moscerini della frutta o zanzare)?

1) SI (proseguire con la domanda F.5.1)
2) NO (passare alla Sezione G)

F.5.1 Quanto frequentemente?

1) meno di 1 volta l'anno
2) 1 volta l'anno
3) più di 1 volta l'anno

Sezione G: informazioni su aspetti odontoiatrici e generali

G.1 Ha otturazioni dentarie effettuate con amalgama (pasta in metallo)? 1) SI 2) NO

G.2 Da quanto tempo è stata effettuata l'ultima otturazione? (anni) |__|__|

G.3 Le sono state rimosse otturazioni? 1) SI 2) NO

G.4 Per quanto tempo le aveva tenute? (anni) |__|__|

G.5 Usa abitualmente masticare chewing gum? 1) SI 2) NO

G.6 Soffre di bruxismo? 1) SI 2) NO

G.7 Ha difficoltà a respirare con il naso? 1) SI 2) NO

G.8 Usa lenti a contatto abitualmente?

1) SI (proseguire con la domanda G.9.1)

2) NO (se è un UOMO ha finito! Se è una DONNA, passare alla sezione H)

G.8.1 Da quanto tempo? (anni) |__|__|

******

La ringraziamo per la pazienza e la collaborazione.

Ci sono altre cose che non le abbiamo chiesto e che pensa siano importanti per la ricerca?

_____

_____

_____

IARC

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Istituto Scientifico Prevenzione Oncologica

Istituto Scientifico della Regione Toscana

Questionario Alimentare – EPIC

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Dipartimento di Scienze Biomediche Metaboliche e Neuroscienze

Progetto EOD

Data di compilazione		Compilazione a cura del personale	
(gg|mm|aa)	|___|___|___|	**Codice ID**	|__|__|__|__|__|

Le domande di questo questionario si riferiscono alla sua alimentazione nell'ultimo anno.

La preghiamo di rispondere a tutte le domande indicate con la freccia " ▶ ".

Ad esempio, se mangia la pizza circa 3 volte al mese e la mangia sempre in pizzeria, risponda come segue:

COME COMPILARE

COSI' ◉ NON COSI' ⊗

▶ **Quante volte mangia la pizza?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.

Settimana S ○ Mese M ○ Anno A ○ 0 1 2 3 4 5 6 7 8 9

Quando mangia PIZZA, di solito la mangia *(risponda in ogni riga annerendo un cerchietto):*	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
▶ - AL TAGLIO	◉	○	○	○	○
▶ - IN PIZZERIA	○	○	○	○	◉
▶ - FATTA IN CASA	◉	○	○	○	○

1 ▶ **Nell'ultimo anno ha seguito una dieta specifica?** ***(risponda annerendo un cerchietto)***

NO ○ SI ○

2 Se SI per quale motivo?

- ○ - per motivi di tipo medico (diabete, pressione alta, colesterolo o trigliceridi alti, ecc.)
- ○ - per dimagrire
- ○ - altro (tipo dieta Macrobiotica o Vegetariana)

specifichi _____

3 ▶ **Normalmente quante volte mangia FUORI CASA (bar, mensa, ristorante) a mezzogiorno?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana 8 9 | Mese A | Anno 0 1 2 1 4 5 4 5 8 9
8 9 A 0 1 2 3 4 5 6 5 6 9

4 ▶ **Normalmente quante volte mangia FUORI CASA (bar, mensa, ristorante) alla sera?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 9 | Mese S | Anno 0 1 0 1 4 5 4 7 6 9
S 9 S 0 1 2 1 4 5 4 7 8 9

Normalmente quando mangia FUORI CASA dove consuma i pasti
(risponda in ogni riga annerendo un cerchietto)

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
5	▶ - MENSA AZIENDALE	○	○	○	○	○
6	▶ - TRATTORIA / RISTORANTE	○	○	○	○	○
7	▶ - PIZZERIA	○	○	○	○	○
8	▶ - BAR	○	○	○	○	○
9	▶ - RISTORANTI ORIENTALI	○	○	○	○	○
10	▶ - RISTORANTI VEGETARIANI	○	○	○	○	○

11 ▶ **Normalmente quando mangia A CASA, con che frequenza cucina Lei personalmente?**

mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
○	○	○	○	○

Pensi sia al pranzo che alla cena

PRIMI PIATTI ASCIUTTI

COME COMPILARE
COSI' ◉ NON COSI' ⊗

12 ▶ **Normalmente quante volte mangia un PRIMO PIATTO DI PASTA o RISO (escluso le minestre in brodo)?**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

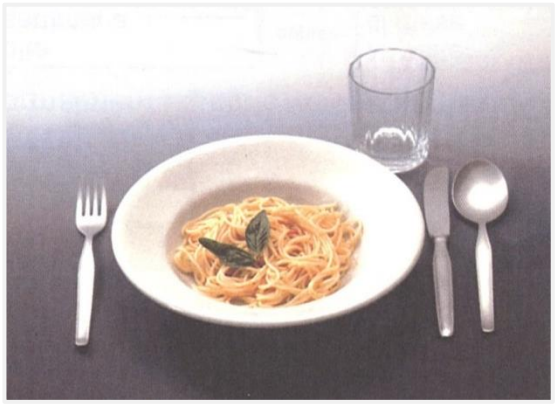
Non scrivere qui.
Settimana S 9 | Mese | Anno S 0 1 0 3 4 5 6 5 6 9
0 1 2 1 4 5 4 5 8 9

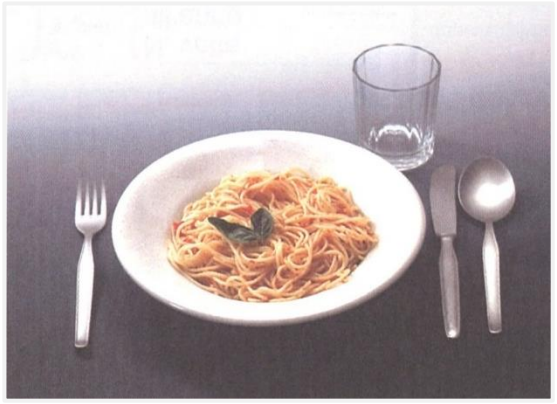
	Normalmente che tipo di PRIMO PIATTO ASCIUTTO mangia? *(risponda in ogni riga annerendo un cerchietto):*	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
13	▶ - PASTASCIUTTA	○	○	○	○	○
14	▶ - PASTA ALL'UOVO	○	○	○	○	○
15	▶ - PASTA RIPIENA o AL FORNO (Tortellini, Cannelloni, Ravioli, Lasagne)	○	○	○	○	○
16	▶ - RISO o RISOTTI	○	○	○	○	○

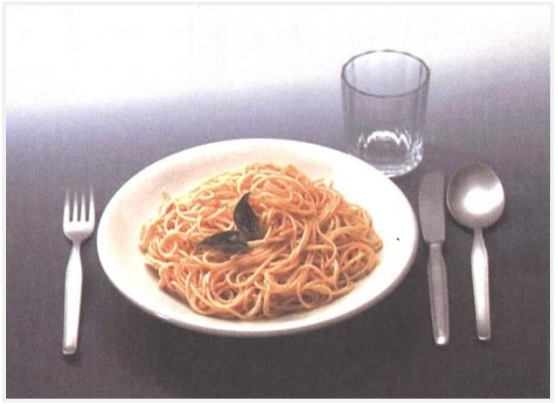
	Quando mangia un PRIMO PIATTO DI PASTASCIUTTA lo condisce *(risponda in ogni riga annerendo un cerchietto):*	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
17	▶ - IN BIANCO	○	○	○	○	○
18	▶ - AL SUGO DI POMODORO	○	○	○	○	○
19	▶ - AL RAGU'	○	○	○	○	○
20	▶ - ALTRI SUGHI	○	○	○	○	○

21 ▶ **Normalmente mangia un piatto di PASTASCIUTTA:**

più piccolo	come questo	tra i due	come questo	tra i due	come questo	più grande
○	○	○	○	○	○	○





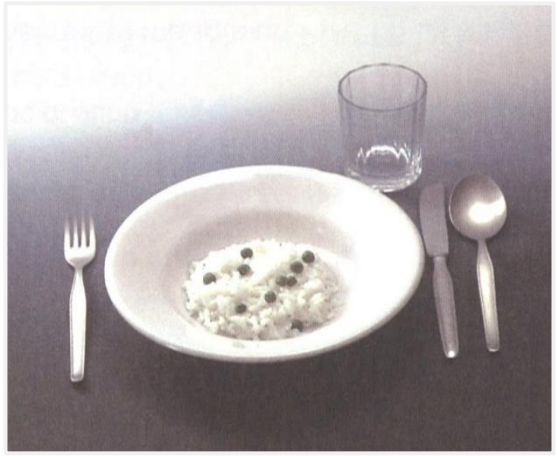


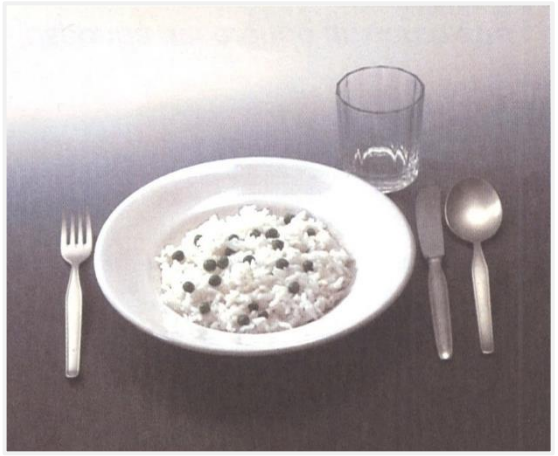
Quando mangia un PRIMO PIATTO DI RISO lo condisce
(risponda in ogni riga annerendo un cerchietto):

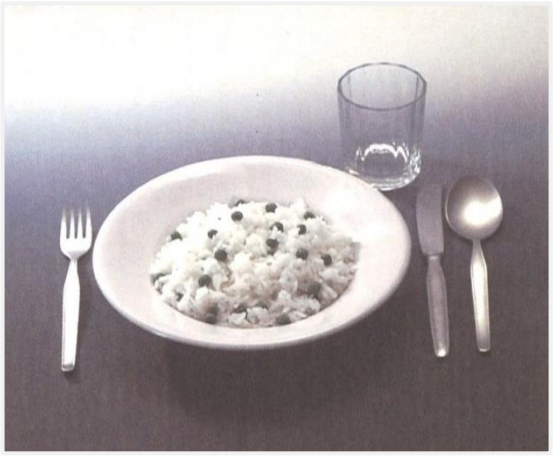
		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
22	▶ - IN BIANCO	○	○	○	○	○
23	▶ - RISOTTO	○	○	○	○	○
24	▶ - INSALATA DI RISO	○	○	○	○	○
25	▶ - ALTRI SUGHI	○	○	○	○	○

26 ▶ **Normalmente mangia un piatto di RISO:**

più piccolo	come questo	tra i due	come questo	tra i due	come questo	più grande
○	○	○	○	○	○	○







27 ▶ **Dopo aver mangiato un primo piatto, SE RIMANE SUGO NEL PIATTO, ha l'abitudine di raccogliere il sugo con il pane?**

mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
○	○	○	○	○

MINESTRE E ZUPPE

COME COMPILARE
COSI' ● NON COSI' ⊗

28 ▶ **Quante volte mangia un PIATTO DI MINESTRA o ZUPPA?**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

Non scrivere qui.
Settimana S
Mese 9
Anno S
0 1 2 1 4 5 4 7 6 9
0 1 2 1 4 5 4 5 8 9

Normalmente che tipo di MINESTRA mangia? ***(risponda in ogni riga annerendo un cerchietto):***

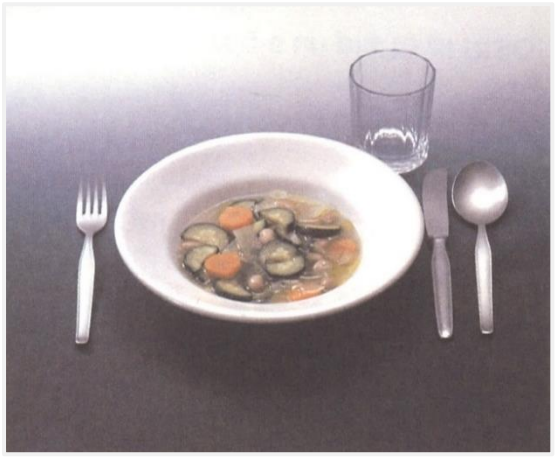
	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
29 ▶ - Minestrone, Zuppe, Passati, Creme di Verduta (anche surgelati)	○	○	○	○	○
30 ▶ - Minestra di fagioli, Ceci, Lenticchie	○	○	○	○	○
31 ▶ - Minestra in brodo	○	○	○	○	○

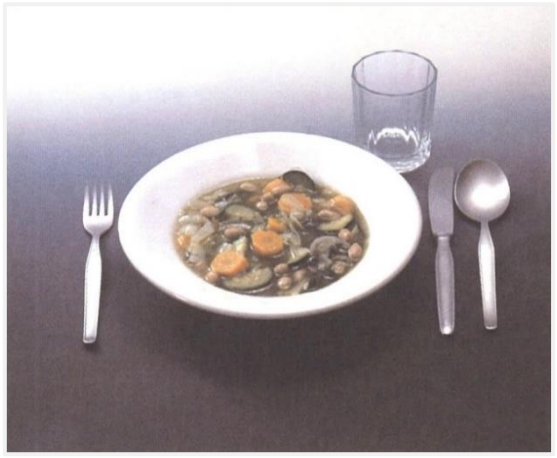
Il BRODO che mangia, è preparato con ***(risponda in ogni riga annerendo un cerchietto):***

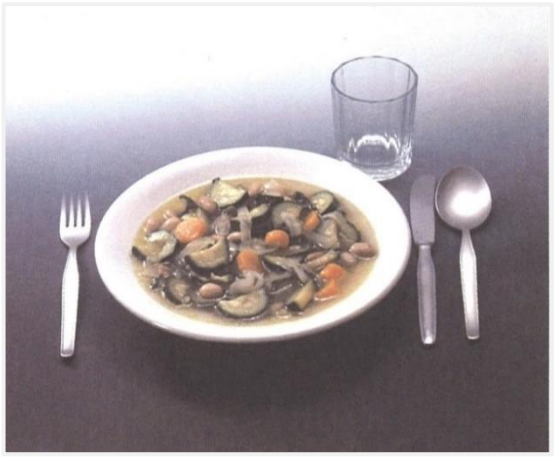
	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
32 ▶ - Brodo di carne / pollo	○	○	○	○	○
33 ▶ - Brodo di dado	○	○	○	○	○

34 ▶ **Normalmente mangia un PIATTO DI MINESTRA** ***(risponda annerendo un cerchietto)*****:**

più piccolo	come questo	tra i due	come questo	tra i due	come questo	più grande
○	○	○	○	○	○	○







Generalmente nelle MINESTRE che mangia c'è anche *(risponda annerendo un cerchietto):*

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
35	▶ - Pasta, Riso, Pane, Semolino	○	○	○	○	○

Normalmente che tipi di GRASSI si usano in casa sua per i PRIMI PIATTI?
(risponda in ogni riga annerendo uno o più cerchietti):

		non so	burro	margarina	olio di oliva	olio di semi	nessuno di questi
36	▶ - Per condire la pasta ed il riso in bianco	○	○	○	○	○	○
37	▶ - Per preparare il sugo di pomodoro	○	○	○	○	○	○
38	▶ - Per preparare il ragù di carne	○	○	○	○	○	○
39	▶ - Per preparare il minestrone	○	○	○	○	○	○

Quando il primo piatto è portato in tavola, aggiunge *(risponda in ogni riga annerendo un cerchietto):*

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
40	▶ - Olio a crudo	○	○	○	○	○
41	▶ - Burro a crudo	○	○	○	○	○
42	▶ - Formaggio grattuggiato	○	○	○	○	○

43 ▶ **Normalmente quante volte mangia POLENTA?**

N. volte alla settimana _____ oppure | N. volte al mese _____ oppure | N. volte all'anno _____ oppure | Mai ○

Non scrivere qui.
Settimana S 9 | Mese 9 | Anno S 0 1 0 1 4 5 6 5 6 9

44 ▶ **Normalmente quante volte mangia PIZZA**

N. volte alla settimana _____ oppure | N. volte al mese _____ oppure | N. volte all'anno _____ oppure | Mai ○

Non scrivere qui.
Settimana S | Mese M | Anno S 0 1 2 1 4 5 4 5 8 9

Quando mangia PIZZA di solito la mangia *(risponda in ogni riga annerendo un cerchietto):*

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
45	▶ - Al taglio	○	○	○	○	○
46	▶ - In pizzeria	○	○	○	○	○
47	▶ - Fatta in casa	○	○	○	○	○

Pensi sia al pranzo che alla cena

CARNE

COME COMPILARE
COSI' ◉ NON COSI' ⊗

48 ▶ **Quante volte mangia CARNE BOVINA? (consideri tutti i tipi: bistecche, fettine, hamburger, arrosti, bolliti, polpette e polpettone, ecc.)**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

Non scrivere qui.
Settimana S 9 | Mese 9 | Anno S 0 1 0 1 4 5 6 5 6 9 | 0 1 2 1 4 5 6 5 8 9

Normalmente che tipo di CARNE BOVINA mangia?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
49	▶ - IN UMIDO (stufato, spezzatino)	○	○	○	○	○
50	▶ - ARROSTO / ROASTBEEF	○	○	○	○	○
51	▶ - BOLLITO (lesso)	○	○	○	○	○
52	▶ - COTOLETTA ALLA MILANESE	○	○	○	○	○
53	▶ - FETTINE ALL'OLIO / BURRO / SCALOPPINE	○	○	○	○	○
54	▶ - BISTECCA ALLA GRIGLIA / AI FERRI	○	○	○	○	○
55	▶ - HAMBURGER	○	○	○	○	○
56	▶ - POLPETTE / POLPETTONE	○	○	○	○	○

57 ▶ **Con quale frequenza mangia CARNE BOVINA BIANCA (Vitello o Vitella di latte)?**

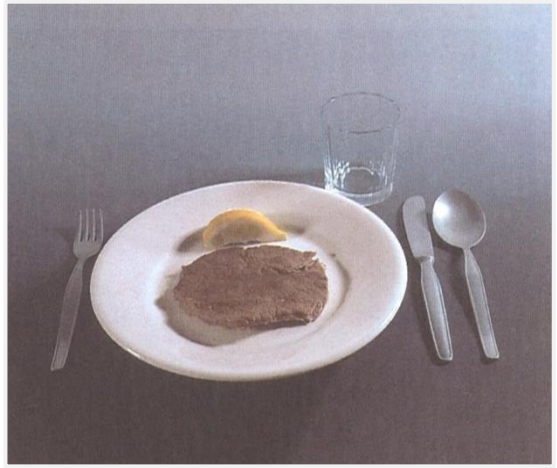
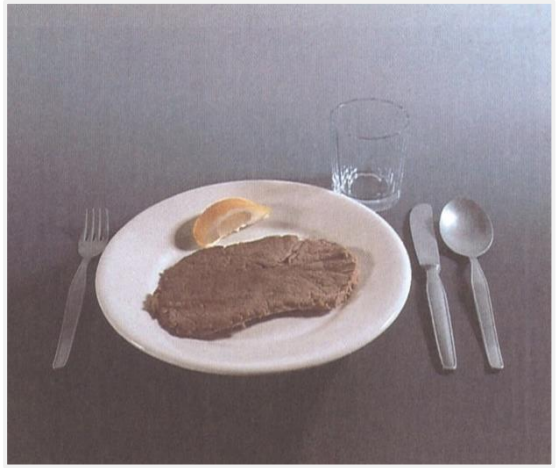
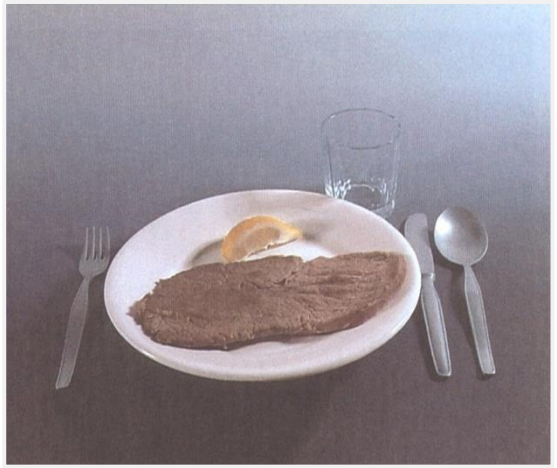
mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
○	○	○	○	○

58 ▶ **Normalmente quando mangia la carne, SCARTA IL GRASSO VISIBILE?**

mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
○	○	○	○	○

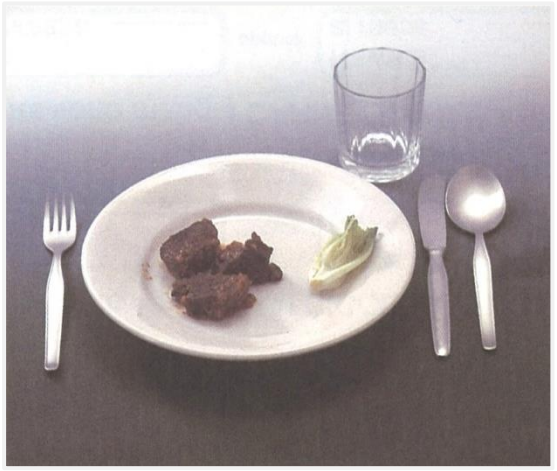
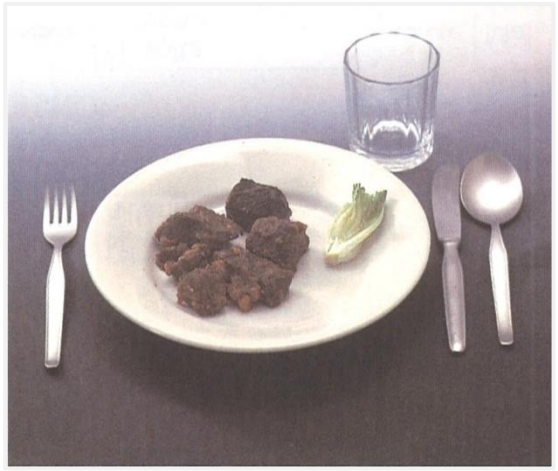
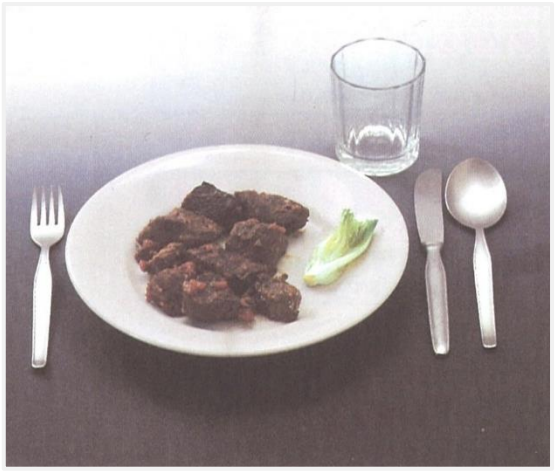
59 ▶ **Normalmente quando mangia FETTINE, BISTECCHE o SCALOPPINE mangia una porzione:**

più piccola ○ | come questa ○ | tra le due ○ | come questa ○ | tra le due ○ | come questa ○ | più grande ○

60 ▶ **Normalmente quando mangia STUFATO, SPEZZATINO o BOLLITO di carne bovina mangia una porzione:**

più piccola ○ | come questa ○ | tra le due ○ | come questa ○ | tra le due ○ | come questa ○ | più grande ○

61 ▶ **Quante volte mangia CARNE DI MAIALE (escluso i salumi)?**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

Non scrivere qui.

Settimana	Mese	Anno								
8	M	S	0	1	2	1	4	5	4	5	8	9

62 ▶ **Quante volte mangia SALSICCE o COTECHINO?**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

Non scrivere qui.

Settimana	Mese	Anno								
S	9	S	0	1	2	1	4	5	4	5	6	9

63 ▶ **Quante volte mangia CARNE DI POLLO o TACCHINO?**

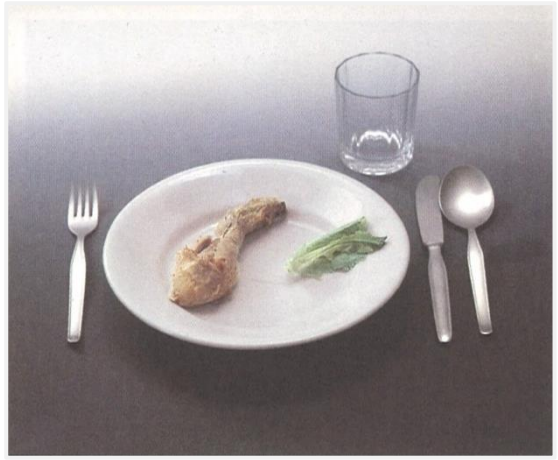
N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

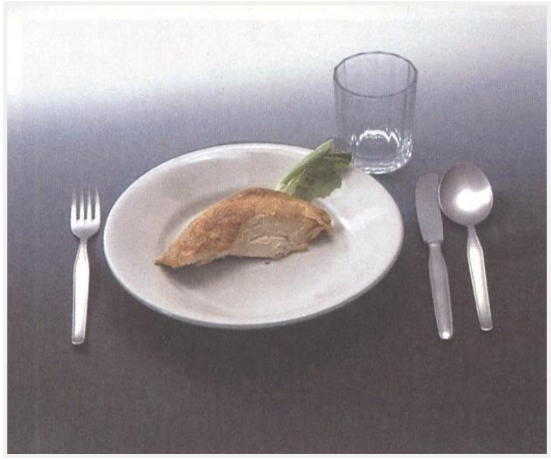
Non scrivere qui.

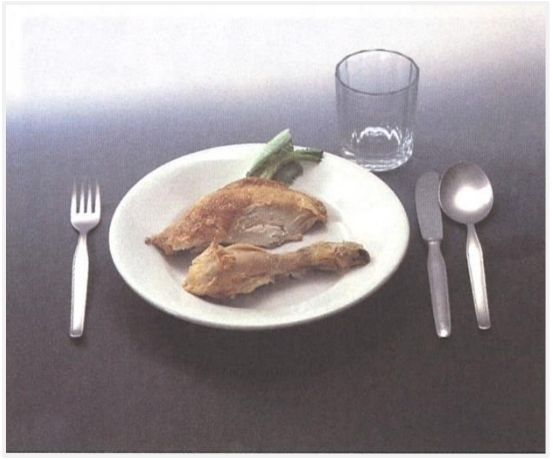
Settimana	Mese	Anno								
8	9	A	0	1	2	1	4	5	4	5	8	9

64 ▶ **Normalmente di POLLO o TACCHINO mangia una porzione:**

più piccola	come questa	tra le due	come questa	tra le due	come questa	più grande
○	○	○	○	○	○	○







65 ▶ **Normalmente quale parte del POLLO o TACCHINO preferisce?**

- la coscia ○	- il petto ○	- altre parti ○	- non ho preferenze particolari ○

66 ▶ **Normalmente, quando mangia pollo o tacchino, SCARTA LA PELLE?**

mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
○	○	○	○	○

67 ▶ **Quante volte mangia CARNE DI CONIGLIO?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana: S 9 S
Mese: 0 1 2 1 4 5 4 7 8 9
Anno: 0 1 0 1 4 5 6 5 6 9

68 ▶ **Quante volte mangia ALTRI TIPI DI CARNE come SELVAGGINA, AGNELLO, CAVALLO, ecc...?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana: S 9 S
Mese: 0 1 2 1 4 5 4 5 8 9
Anno: 0 1 2 1 4 5 4 5 8 9

69 ▶ **Quante volte mangia FEGATO (di manzo, vitello, maiale, pollo, coniglio)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana: S 9 S
Mese: 0 1 2 1 4 5 4 7 6 9
Anno: 0 1 2 1 4 5 4 5 8 9

70 ▶ **Quante volte mangia FRATTAGLIE (trippa, cervello, rognone, ecc…)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana: S 9 S
Mese: 0 1 2 1 4 5 4 5 8 9
Anno: 0 1 0 1 4 5 6 5 6 9

71 ▶ **Quante volte mangia CARNE IN SCATOLA?**

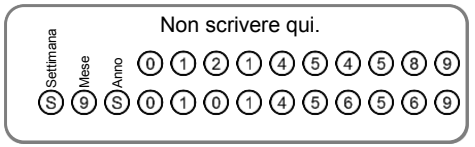
N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana: S M S
Mese: 0 1 2 1 4 5 4 5 8 9
Anno: 0 1 2 1 4 5 4 5 8 9

PESCE

72 ▶ **Quante volte mangia MOLLUSCHI, FRUTTI DI MARE o CROSTACEI (inclusi i condimenti dei primi piatti)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

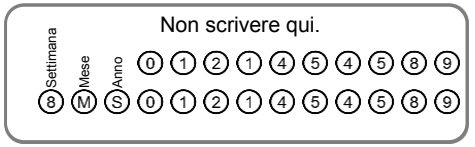


Normalmente quali tipi di MOLLUSCHI, FRUTTI DI MARE o CROSTACEI mangia?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
73	▶ - GAMBERI, GAMBERONI, SCAMPI	○	○	○	○	○
74	▶ - POLPI, SEPPIE, CALAMARI	○	○	○	○	○
75	▶ - COZZE, VONGOLE	○	○	○	○	○

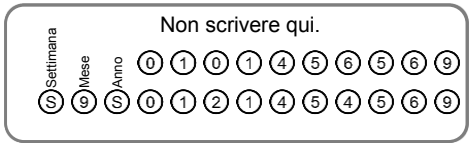
76 ▶ **Quante volte mangia PESCE CONSERVATO come Baccalà o Stoccafisso?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○



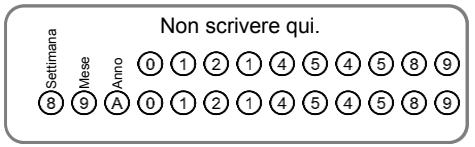
77 ▶ **Quante volte mangia un secondo di PESCE IN SCATOLA (Tonno, Sgombri, Sardine, Alici)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○



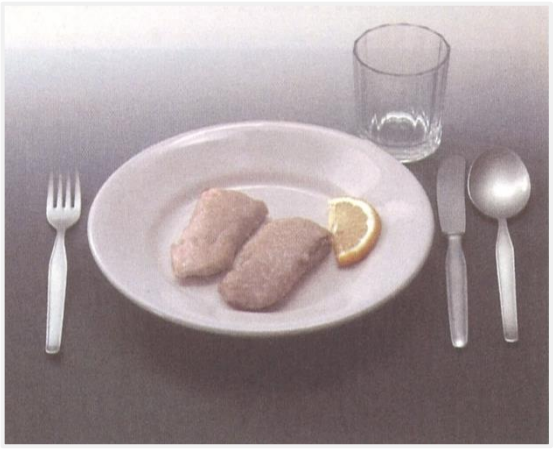
78 ▶ **Quante volte mangia un secondo di PESCE FRESCO o SURGELATO?**

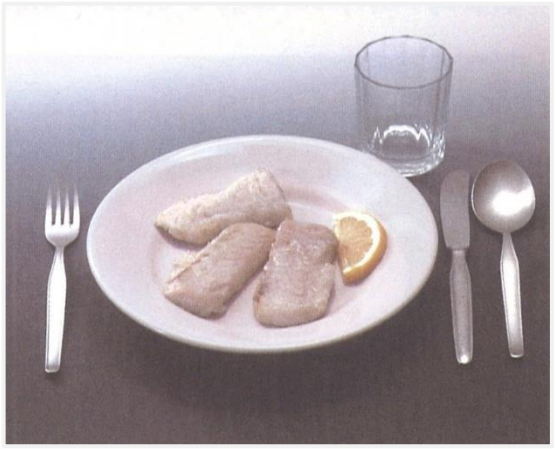
N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

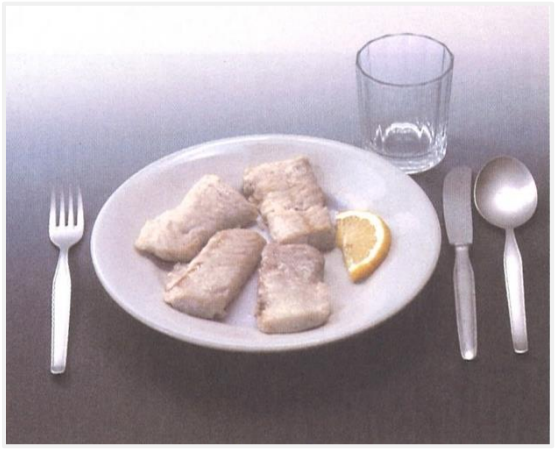


79 ▶ **Normalmente di PESCE FRESCO o SURGELATO mangia una porzione:**

più piccola	come questa	tra le due	come questa	tra le due	come questa	più grande
○	○	○	○	○	○	○







Normalmente quali tipi di PESCE FRESCO o SURGELATO mangia ***(risponda in ogni riga annerendo un cerchietto):***	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
80 ▶ - NASELLO, PALOMBO, MERLUZZO compresi i bastoncini	○	○	○	○	○
81 ▶ - SOGLIOLA, PLASTESSA	○	○	○	○	○
82 ▶ - SARDINE, SGOMBRI, ALICI	○	○	○	○	○
83 ▶ - TROTA od ALTRO PESCE DI ACQUA DOLCE	○	○	○	○	○
84 ▶ - TRANCIO DI PESCE SPADA, TONNO, SALMONE	○	○	○	○	○
85 ▶ - ALTRI TIPI	○	○	○	○	○

Normalmente quando mangia PESCE lo mangia ***(risponda in ogni riga annerendo un cerchietto):***	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
86 ▶ - BOLLITO	○	○	○	○	○
87 ▶ - ARROSTO / IN UMIDO	○	○	○	○	○
88 ▶ - FRITTO	○	○	○	○	○
89 ▶ - ALLA GRIGLIA	○	○	○	○	○

VERDURA CRUDA

Pensi sia al pranzo che alla cena – Se ha l'abitudine di consumare insalata miste,
La preghiamo di rispondere alle seguenti domande considerando le singole verdure, una per una.

COME COMPILARE
COSI' ◉ NON COSI' ⊗

90 ▶ **Quante volte mangia POMODORI in stagione *(consideri anche quelli messi nell'insalata mista)*?**

N. volte alla settimana _____ oppure | N. volte al mese _____ oppure | Raramente ○ oppure | Mai ○

Non scrivere qui.
Settimana 8 9 A | Mese 0 1 0 1 | Anno 4 5 6 7 6 9

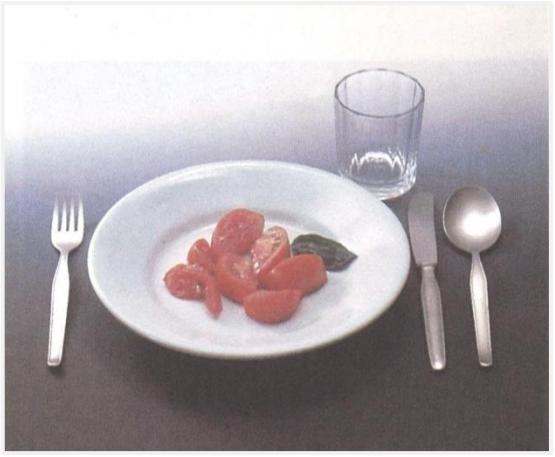
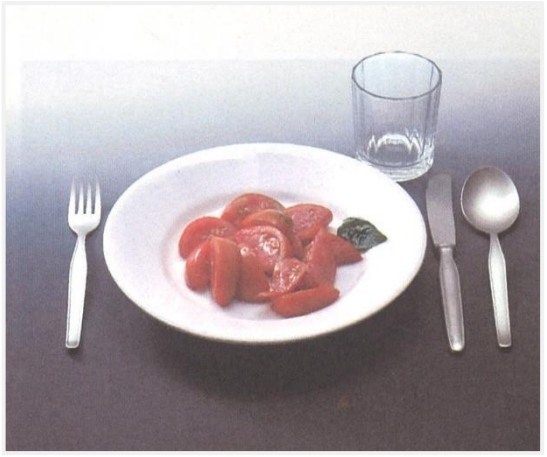
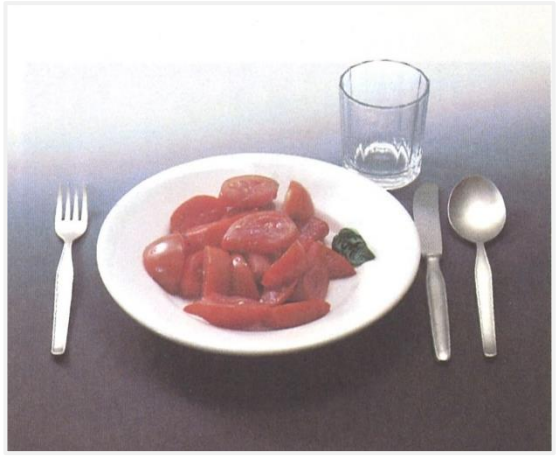
91 ▶ **Quante volte mangia POMODORI fuori stagione *(consideri anche quelli messi nell'insalata mista)*?**

N. volte alla settimana _____ oppure | N. volte al mese _____ oppure | Raramente ○ oppure | Mai ○

Non scrivere qui.
Settimana 8 9 A | Mese 0 1 0 1 | Anno 4 5 4 7 8 9

92 ▶ **Normalmente di POMODORI mangia una porzione:**

più piccola ○ | come questa ○ | tra le due ○ | come questa ○ | tra le due ○ | come questa ○ | più grande ○

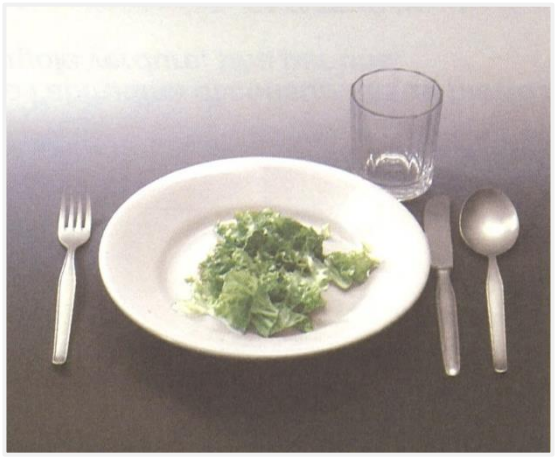
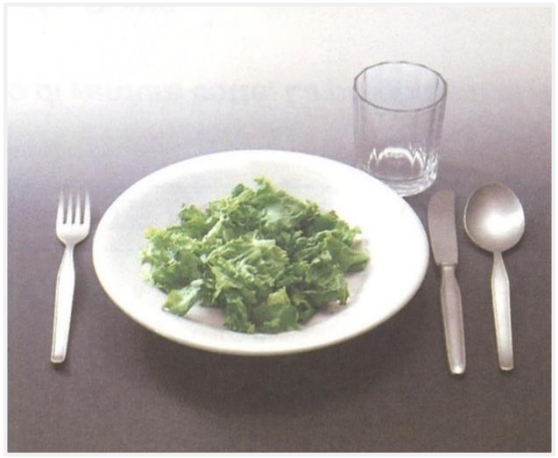
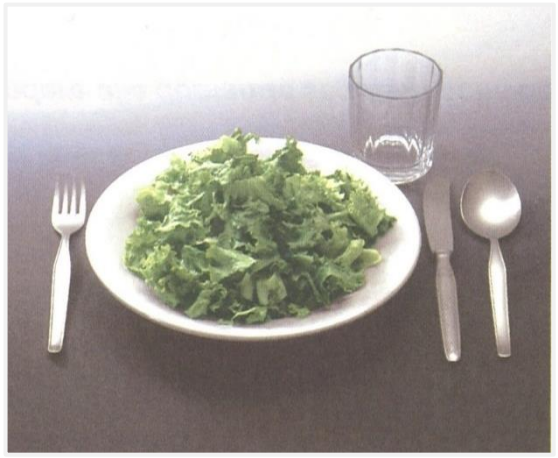
93 ▶ **Quante volte mangia INSALATA (lattura, radicchio, cicoria, o altra insalata a foglia)** ***(consideri anche quella messa nell'insalata mista)*?**

N. volte alla settimana _____ oppure | N. volte al mese _____ oppure | Raramente ○ oppure | Mai ○

Non scrivere qui.
Settimana 8 9 A | Mese 0 1 0 1 | Anno 4 3 4 7 6 9

94 ▶ **Normalmente mangia un piatto di INSALATA:**

più piccolo	come questo	tra i due	come questo	tra i due	come questo	più grande
○	○	○	○	○	○	○

95 ▶ **Quante volte mangia PEPERONI CRUDI *(consideri anche quelli messi nell'insalata mista)*?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana 8 Mese 9 Anno A 0 1 0 3 4 3 6 7 8 9

96 ▶ **Quante volte mangia CIPOLLE o CIPOLLINE FRESCHE *(consideri anche quelle messe nell'insalata mista)*?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana 8 Mese 9 Anno A 0 1 0 1 4 3 4 7 8 9

97 ▶ **In stagione quante volte mangia CARCIOFI, FINOCCHI o SEDANI in pinzimonio o nell'insalata mista?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana 8 Mese 9 Anno A 0 1 0 1 4 3 6 7 6 9

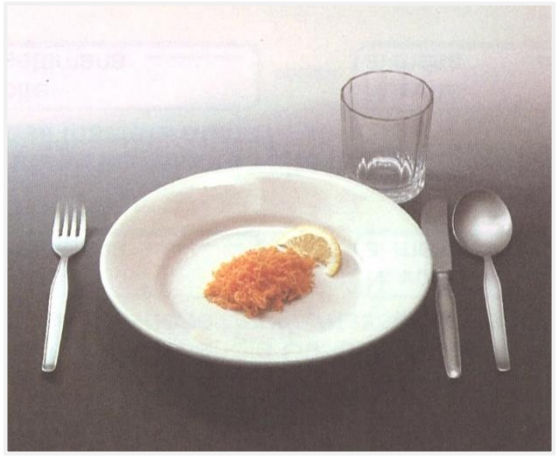
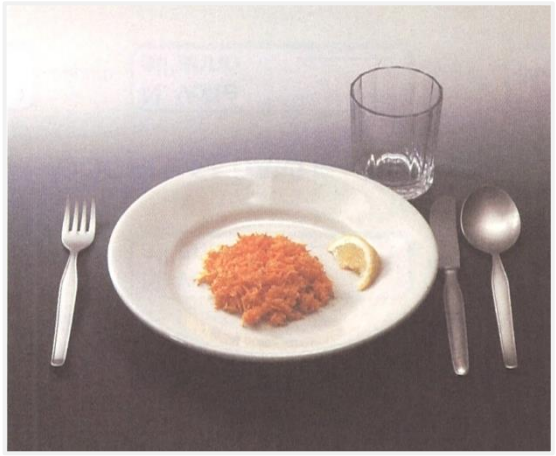
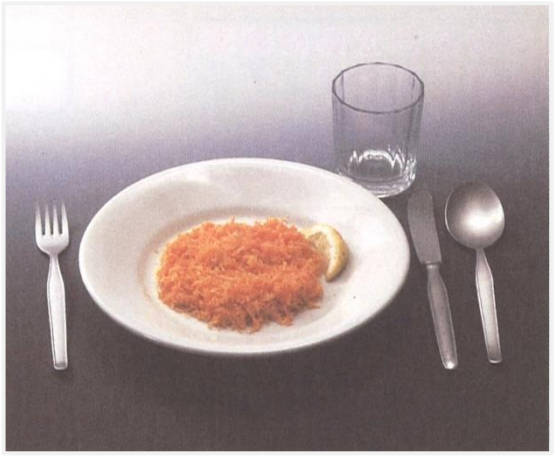
98 ▶ **Quante volte mangia CAROTE CRUDE *(consideri anche quelle messe nell'insalata mista)*?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana 8 Mese M Anno A 0 1 0 1 4 3 4 7 8 9

99 ▶ **Normalmente mangia un piatto di CAROTE CRUDE:**

più piccolo	come questo	tra i due	come questo	tra i due	come questo	più grande
○	○	○	○	○	○	○

100 ▶ **Normalmente, con che OLIO condisce la VERDURA CRUDA? *(risponda annerendo uno o più cerchietti)*:**

- NESSUN TIPO DI OLIO ○
- OLIO D'OLIVA ○
- OLIO DI SEMI ○
- non mangio mai verdura cruda ○

Se usa olio di semi indichi il tipo di olio di semi

arachidi	girasole	mais	soia	altri semi	non so
○	○	○	○	○	○

PATATE E VERDURA COTTA

Se ha l'abitudine di consumare un piatto misto di verdure cotte, La preghiamo di rispondere alle seguenti domande considerando le singole verdure, una per una.

COME COMPILARE
COSI' ◉ NON COSI' ⊗

101 ▶ **Quante volte mangia PATATE (Fritte, Lesse, Arrosto, Purè)?**

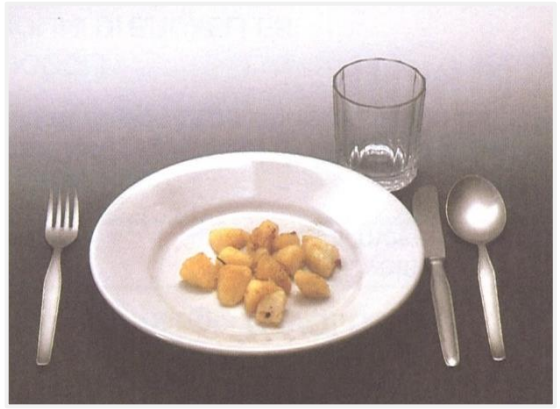
N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

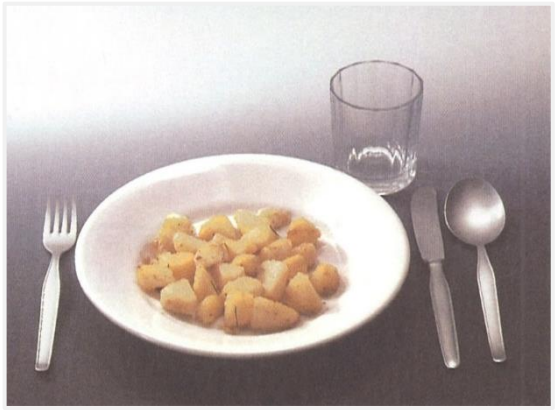
Non scrivere qui.

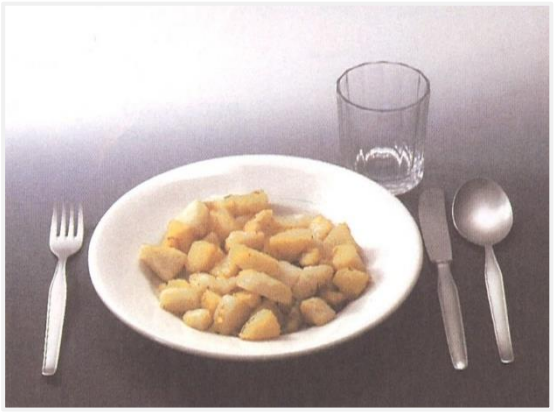
Settimana	8	8	A	0	1	0	0	4	3	6	6	6	9
Mese				0	1	1	0	4	3	6	4	8	9
Anno													

102 ▶ **Normalmente di PATATE mangia una porzione (consideri le patate arrosto come esempio):**

più piccola ○ | come questa ○ | tra le due ○ | come questa ○ | tra le due ○ | come questa ○ | più grande ○







103 ▶ **Quante volte mangia SFORMATI o PASTICCI o TORTE DI VERDURA (tutti i tipi)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui. Settimana Mese Anno 0 1 0 1 4 3 4 7 8 9 / 8 9 A 0 1 0 1 4 3 4 7 8 9

104 ▶ **Quante volte mangia FAGLIOLI o CECI (Secchi, Freschi, In scatola)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui. Settimana Mese Anno 0 1 0 1 4 3 6 7 6 9 / 8 9 A 0 1 0 1 4 3 4 7 6 9

105 ▶ **Quante volte mangia PISELLI (Feschi, Surgelati, In scatola)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui. Settimana Mese Anno 0 1 0 1 4 3 4 7 8 9 / 8 9 A 0 1 0 1 4 3 4 7 8 9

106 ▶ **Quante volte mangia FUNGHI COTTI (tutti i tipi, anche coltivati)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui. Settimana Mese Anno 0 1 0 1 4 3 4 7 6 9 / 8 9 A 0 1 0 1 4 3 4 7 8 9

107 ▶ **Quante volte mangia CIPOLLE, CIPOLLINE o PORRI COTTI?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui. Settimana Mese Anno 0 1 0 1 4 3 4 7 8 9 / 8 9 A 0 1 0 3 4 3 6 7 8 9

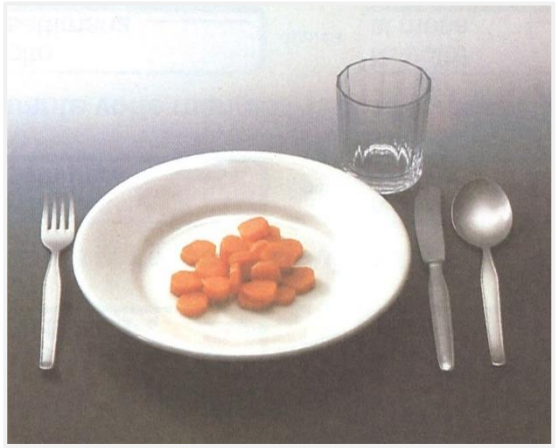
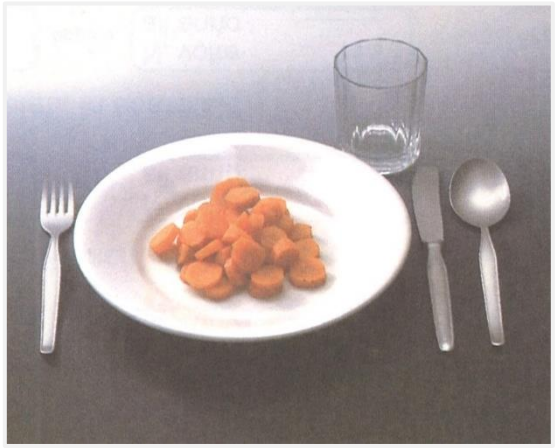
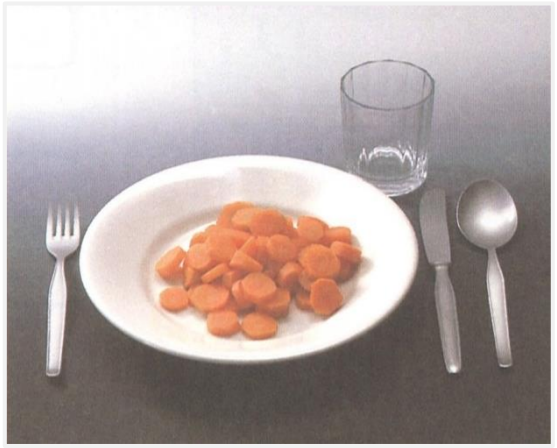
108 ▶ **Quante volte mangia CAROTE COTTE?**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

Non scrivere qui.
Settimana 8 9 A | Mese 0 1 | Anno 0 1 0 1 4 3 4 7 8 9

109 ▶ **Normalmente mangia una porzione di CAROTE COTTE:**

più piccola	come questa	tra le due	come questa	tra le due	come questa	più grande
○	○	○	○	○	○	○

110 ▶ **Quante volte mangia CAVOLO?**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

Non scrivere qui.
Settimana 8 9 A | Mese 0 1 | Anno 0 1 0 1 4 3 6 7 6 9

Normalmente quali tipi di CAVOLO mangia?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
111	▶ - BROCCOLI	○	○	○	○	○
112	▶ - CAVOLINI DI BRUXELLES	○	○	○	○	○
113	▶ - CAVOLFIORE	○	○	○	○	○
114	▶ - CIME DI RAPA	○	○	○	○	○
115	▶ - VERZE	○	○	○	○	○
116	▶ - CAVOLO NERO	○	○	○	○	○

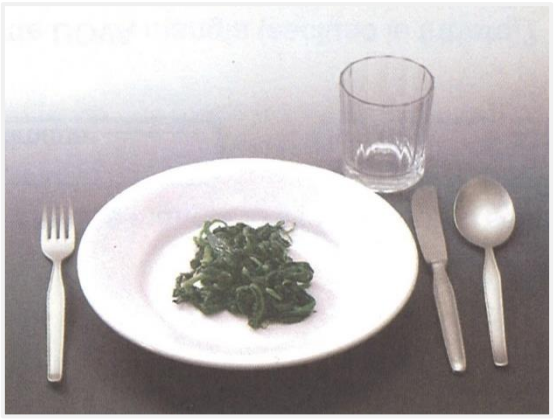
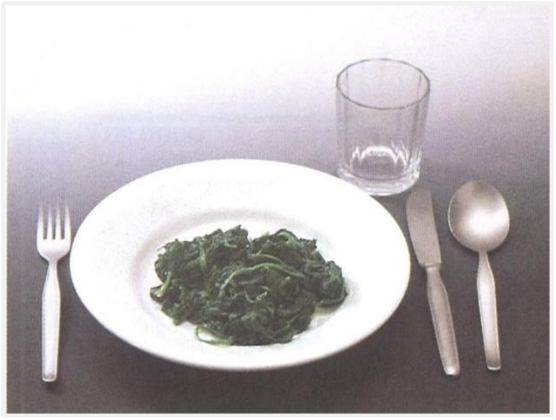
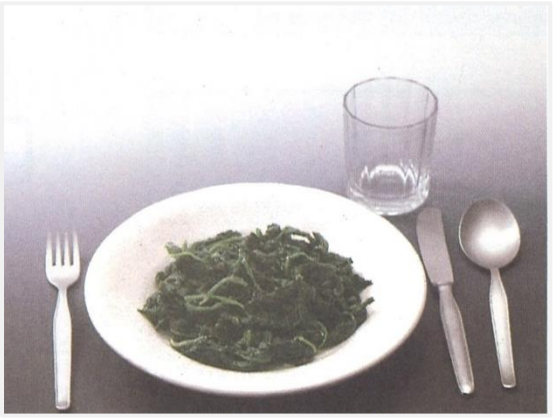
117 ▶ **Quante volte mangia SPINACI, BIETOLE, COSTE, ERBETTE COTTE?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana 8 Mese M Anno A 0 1 0 1 4 3 4 7 8 9

118 ▶ **Normalmente mangia una porzione di SPINACI, BIETOLE, COSTE, ERBETTE COTTE:**

più piccola ○ come questa ○ tra le due ○ come questa ○ tra le due ○ come questa ○ più grande ○

119 ▶ **Quante volte mangia PEPERONI COTTI?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S Mese 9 Anno A 0 1 2 1 4 3 6 7 6 9

120 ▶ **Quante volte mangia MELANZANE, ZUCCHINE, FAGIOLINI COTTI?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S Mese 9 Anno A 0 1 2 1 4 3 4 7 8 9

121 ▶ **Quante volte mangia CARCIOFI o FINOCCHI COTTI?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S Mese 9 Anno A 0 1 2 1 4 3 6 7 6 9

122 ▶ **Quante volte mangia BARBABIETOLE ROSSE (BARBE ROSSE)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S Mese 9 Anno A 0 1 2 1 4 3 4 7 8 9

Normalmente le VERDURE COTTE che mangia sono cucinate
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
123	▶ - LESSE IN ACQUA	○	○	○	○	○
124	▶ - IN UMIDO, TRIFOLATE	○	○	○	○	○
125	▶ - ARROSTO	○	○	○	○	○
126	▶ - FRITTE	○	○	○	○	○

127 ▶ **Normalmente, con che OLIO condisce la VERDURA CRUDA? *(risponda annerendo uno o più cerchietti)*:**

- NESSUN TIPO DI OLIO ○ - OLIO D'OLIVA ○ - OLIO DI SEMI ○

- non mangio mai verdura cruda ○

Se usa olio di semi indichi il tipo di olio di semi

arachidi	girasole	mais	soia	altri semi	non so
○	○	○	○	○	○

UOVA

COME COMPILARE
COSI' ◉ NON COSI' ⊗

128 ▶ **Quante volte mangia FRITTATA (con o senza verdura)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 0 1 2 1 4 3 4 7 6 9
Mese 9 Anno A 0 1 2 1 4 3 4 7 8 9

129 ▶ **Quante UOVA mangia (escluso le frittate)?**

N. uova alla settimana _____ oppure N. uova al mese _____ oppure N. uova all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 0 1 2 1 4 3 4 7 8 9
Mese 9 Anno A 0 1 2 3 4 3 6 7 8 9

130 ▶ **Quante volte mangia MAIONESE (consideri anche l'INSALATA RUSSA)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 0 1 2 1 4 3 4 7 8 9
Mese 9 Anno A 0 1 2 1 4 3 4 7 8 9

PANINI IMBOTTITI

COME COMPILARE
COSI' ◉ NON COSI' ⊗

Pensi sia al pranzo che agli spuntini

131 ▶ **Quanto PANINI IMBOTTITI, TOAST o TRAMEZZINI mangia?**

N. panini alla settimana _____	oppure	N. panini al mese _____	oppure	N. panini all'anno _____	oppure	Mai ○

Non scrivere qui.
Settimana S | Mese 9 | Anno A
0 1 2 1 4 3 4 7 8 9
S 9 A 0 1 2 1 4 3 6 7 6 9

132 ▶ **Normalmente il PANINO IMBOTTITO che mangia è:**

più piccolo	come questo	tra i due	come questo	tra i due	come questo	più grande
○	○	○	○	○	○	○



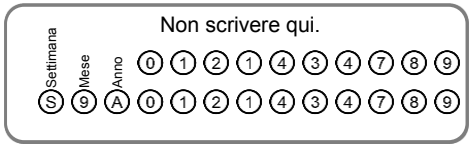
Quando mangia PANINI, di solito con cosa sono imbottiti?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
133	▶ - SALUMI / AFFETTATI	○	○	○	○	○
134	▶ - FORMAGGIO	○	○	○	○	○
135	▶ - VERDURA	○	○	○	○	○

AFFETTATI E ANTIPASTI

136 ▶ **Quante volte mangia SALUMI o AFFETTATI, esclusi quelli dei panini imbottiti?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○



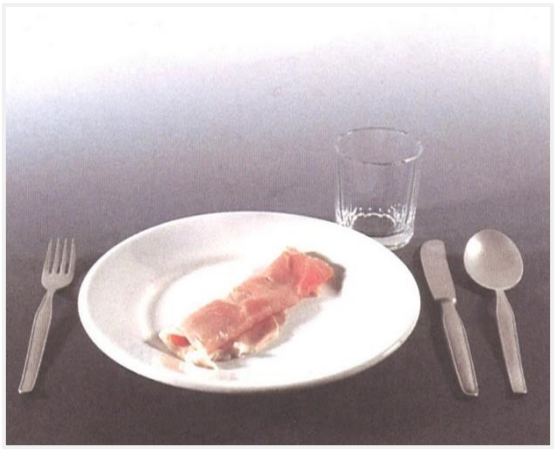
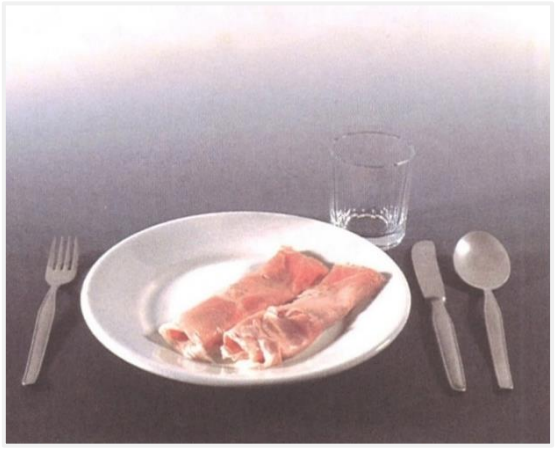
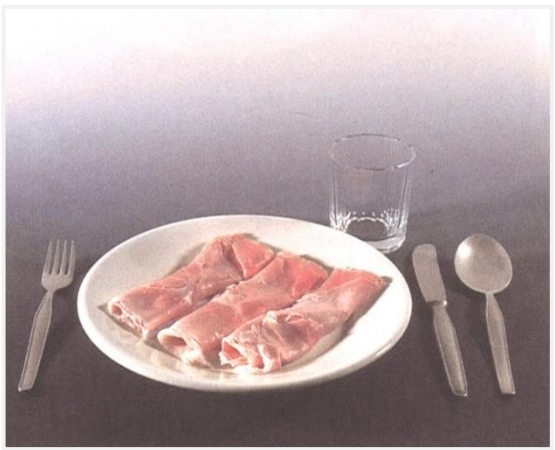
	Normalmente che tipi di SALUMI o AFFETTATI consuma ***(risponda in ogni riga annerendo un cerchietto):***	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
137	▶ - PROSCIUTTO COTTO	○	○	○	○	○
138	▶ - PROSCIUTTO CRUDO	○	○	○	○	○
139	▶ - SALAME (tutti i tipi)	○	○	○	○	○
140	▶ - MORTADELLA, WURSTEL	○	○	○	○	○
141	▶ - BRESAOLA	○	○	○	○	○
142	▶ - SOPPRESSATA, COPPA, FINOCCHIONA, CAPOCOLLO, PANCETTA, SPECK	○	○	○	○	○
143	▶ - ALTRI TIPI	○	○	○	○	○

144 ▶ **Normalmente quando mangia prosciutto cotto, crudo o speck, SCARTA IL GRASSO?**

mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
○	○	○	○	○

145 ▶ **Normalmente di AFFETTATO mangia una porzione:**

più piccola	come questa	tra le due	come questa	tra le due	come questa	più grande
○	○	○	○	○	○	○

146 ▶ **Quante volte mangia un ANTIPASTO SOTT'OLIO? (Acciughe, Funghi, Carciofini ecc...)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 9 Mese A 9 Anno 0 1 2 1 4 5 6 7 6 9

147 ▶ **Quante volte mangia SOTTACETI (sia come antipasti che come contorno)?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure N. volte all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S M Mese A Anno 0 1 2 1 4 5 4 7 8 9

FORMAGGI

COME COMPILARE
COSI' ◉ NON COSI' ⊗

Abbiamo diviso i Formaggi in due liste, una con i Formaggi Stagionati, la seconda con i Formaggi a Pasta Molle. Pensi al Formaggio sia come secondo piatto che come fine pasto (non consideri quello dei Panini Imbottiti).

148 ▶ **Quante volte mangia FORMAGGI STAGIONATI?**

N. volte alla settimana _____ oppure | N. volte al mese _____ oppure | N. volte all'anno _____ oppure | Mai ○

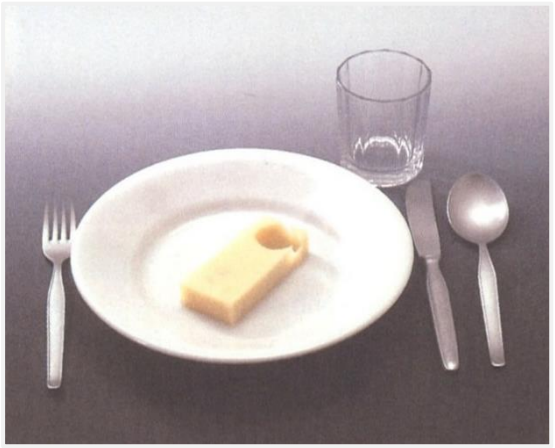
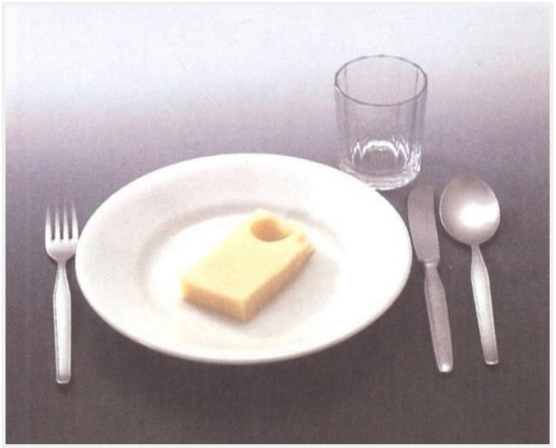
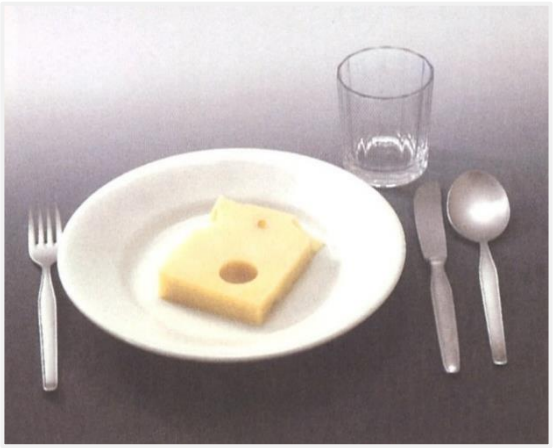
Non scrivere qui.
Settimana S 9 | Mese A | Anno 0 1 2 1 4 5 6 7 6 9

Normalmente che tipi di FORMAGGI STAGIONATI consuma?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
149	▶ - FONTINA, FONTAL, TOMA	○	○	○	○	○
150	▶ - PECORINO, CACIOTTA TOSCANA	○	○	○	○	○
151	▶ - EMMENTAL, GROVIERA, EDAM	○	○	○	○	○
152	▶ - CACIOCAVALLO, PROVOLONE	○	○	○	○	○
153	▶ - PARMIGIANO, GRANA (escluso quello grattuggiato)	○	○	○	○	○
154	▶ - ALTRI TIPI	○	○	○	○	○

155 ▶ **Quando mangia un FORMAGGIO STAGIONATO, la sua porzione è:**

più piccola	come questa	tra le due	come questa	tra le due	come questa	più grande
○	○	○	○	○	○	○

156 ▶ **Quante volte mangia FORMAGGI A PASTA MOLLE?**

N. volte alla settimana _____	oppure	N. volte al mese _____	oppure	N. volte all'anno _____	oppure	Mai ○

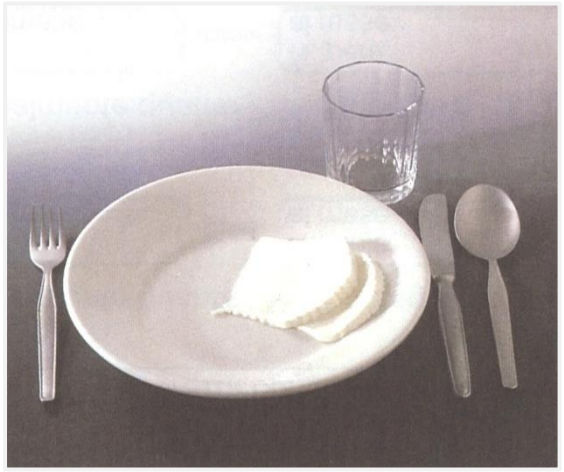
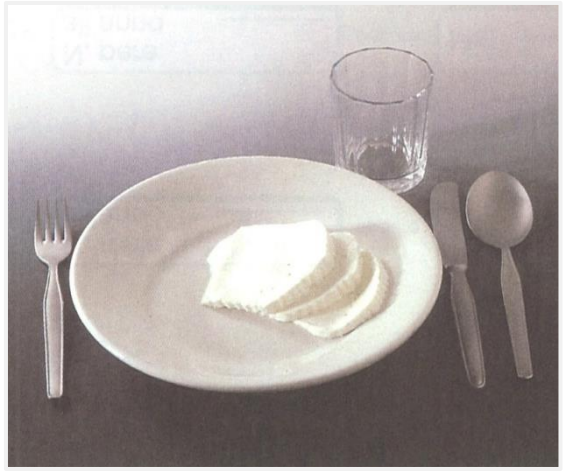
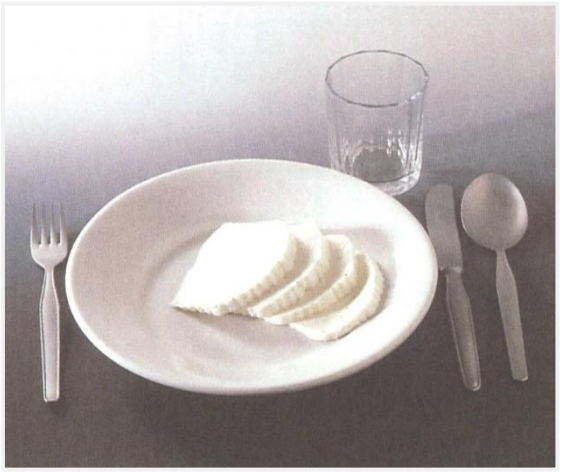
Non scrivere qui.
Settimana S 0 1 2 1 4 5 4 7 8 9
Mese 9
Anno A 0 1 2 1 4 5 4 7 8 9

Normalmente che tipi di FORMAGGI A PASTA MOLLE consuma?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
157	▶ - SOTTILETTE, FORMAGGINI	○	○	○	○	○
158	▶ - PHILADELFIA, FORMAGGI ALLE ERBE	○	○	○	○	○
159	▶ - CRESCENZA, CERTOSINO, STRACCHINO	○	○	○	○	○
160	▶ - MOZZARELLA, FIORDILATTE	○	○	○	○	○
161	▶ - TALEGGIO, BEL PAESE, BRIE	○	○	○	○	○
162	▶ - GORGONZOLA	○	○	○	○	○
163	▶ - ROBIOLA, TOMINI	○	○	○	○	○
164	▶ - RICOTTA	○	○	○	○	○
165	▶ - ALTRI TIPI	○	○	○	○	○

166 ▶ **Quando mangia un FORMAGGIO A PASTA MOLLE, la sua porzione è:**

più piccola	come questa	tra le due	come questa	tra le due	come questa	più grande
○	○	○	○	○	○	○

FRUTTA

COME COMPILARE
COSI' ● NON COSI' ⊗

Pensi anche alla frutta consumata fuori pasto

167 ▶ **Normalmente quante MELE mangia?**

N. mele alla settimana _____ oppure N. mele al mese _____ oppure N. mele all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana 9 9 Mese 9 9 Anno 0 1 1 2 4 5 5 7 6 9

168 ▶ **Normalmente quante PERE mangia?**

N. pere alla settimana _____ oppure N. pere al mese _____ oppure N. pere all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 9 Mese A 0 Anno 1 2 1 4 5 4 7 8 9

169 ▶ **Normalmente quante BANANE mangia?**

N. banane alla settimana _____ oppure N. banane al mese _____ oppure N. banane all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 9 Mese A 0 Anno 1 2 1 4 5 6 7 6 9

170 ▶ **Normalmente quanti KIWI mangia?**

N. kiwi alla settimana _____ oppure N. kiwi al mese _____ oppure N. kiwi all'anno _____ oppure Mai ○

Non scrivere qui.
Settimana S 9 Mese A 0 Anno 1 2 1 4 5 4 7 8 9

Adesso segue una lista di frutta che è disponibile soprattutto in una particolare "stagione". Indichi la frequenza di consumo in quel periodo

171 ▶ **In stagione, quante ARANCE o POMPELMI mangia (escluso le SPREMUTE)?**

N. arance alla settimana _____ oppure N. arance al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui.
Settimana S 9 Mese A 0 Anno 1 2 1 4 5 4 7 6 9

172 ▶ **In stagione, quanti MANDARINI o MANDARANCI mangia?**

N. mandarini alla settimana _____ oppure N. mandarini al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui.
Settimana S 9 Mese A 0 Anno 1 2 1 4 5 6 7 6 9

173 ▶ **In stagione, quanti grappoli di UVA mangia *(consideri un grappolo piccolo)*?**

N. grappoli alla settimana _____ oppure N. grappoli al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 0 1 2 1 4 5 4 7 8 9 · Mese M · Anno A 0 1 2 1 4 5 4 7 8 9

174 ▶ **In stagione, quante PESCHE o PESCHENOCI mangia?**

N. pesche alla settimana _____ oppure N. pesche al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 3 4 5 6 7 6 9

175 ▶ **In stagione, quante ALBICOCCHE mangia?**

N. albicocche alla settimana _____ oppure N. albicocche al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 1 4 5 4 7 8 9

176 ▶ **In stagione, quante SUSINE mangia?**

N. susine alla settimana _____ oppure N. susine al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 1 4 5 4 7 6 9

177 ▶ **In stagione, quante tazze di FRAGOLE mangia?**

N. tazze alla settimana _____ oppure N. tazze al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 1 4 5 4 7 8 9

178 ▶ **In stagione, quante fette di MELONE (POPONE) mangia?**

N. fette alla settimana _____ oppure N. fette al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 1 4 5 4 7 6 9

179 ▶ **Quante tazze di MACEDONIA mangia?**

N. tazze alla settimana _____ oppure N. tazze al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 3 4 5 6 7 8 9

180 ▶ **Quante volte mangia FRUTTA SECCA del tipo PRUGNE e FICHI SECCHI, DATTERI?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 1 4 5 4 7 8 9

181 ▶ **Quante volte mangia NOCI, NOCCIOLE, MANDORLE, ARACHIDI?**

N. volte alla settimana _____ oppure N. volte al mese _____ oppure Raramente ○ oppure Mai ○

Non scrivere qui. Settimana S 9 · Mese 9 · Anno A 0 1 2 1 4 5 6 7 6 9

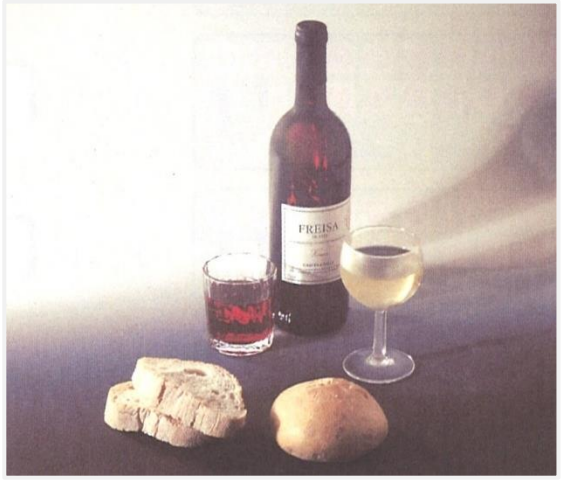
PANE, VINO

COME COMPILARE
COSI' ◉ NON COSI' ⊗

Nella foto ci sono un PANINO, due FETTE di PANE e due bicchieri di VINO di uguale contenuto

Un PACCHETTO DI CRACKERS o GRISSINI equivale ad un panino

Pensi anche al consumo fuori pasto.



182 ▶ **Quanti PANINI, FETTE di PANE o PACCHETTI DI CRACKERS mangia?**

N. pezzi al giorno _____ oppure N. pezzi alla settimana _____ oppure N. pezzi al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 0 1 2 1 4 5 4 7 8 9
Mese M
Anno A 0 1 2 1 4 5 4 7 8 9

Normalmente che tipo di PANE mangia?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
183	▶ - Panini o Pane condito di tipo bianco	○	○	○	○	○
184	▶ - Pane comune bianco (di pezzatura grossa)	○	○	○	○	○
185	▶ - Pane integrale	○	○	○	○	○
186	▶ - Grissini, Crackers	○	○	○	○	○
187	▶ - Altri tipi di Pane	○	○	○	○	○

188 ▶ **Quanti BICCHIERI di VINO beve?**

N. bicchieri al giorno _____ oppure N. bicchieri alla settimana _____ oppure N. bicchieri al mese _____ oppure Rara-mente ○ oppure Mai ○

Non scrivere qui.
Settimana S 9
Mese 9
Anno A 0 1 2 1 4 5 6 7 6 9

Normalmente che tipo di VINO beve?
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
189	▶ - Vino rosso	○	○	○	○	○
190	▶ - Vino bianco	○	○	○	○	○

191 ▶ Quanti BICCHIERI di APERITIVI o VINI LIQUOROSI beve (es.: Martini, Vermuth, Porto, Vin Santo, ecc…)?

N. bicchieri al giorno _____ oppure N. bicchieri alla settimana _____ oppure N. bicchieri al mese _____ oppure Rara-mente ○ oppure Mai ○

Non scrivere qui.
Settimana Mese Anno
0 1 2 1 4 5 4 7 8 9
S 9 A 0 1 2 1 4 5 4 7 8 9

192 ▶ Quanti BICCHIERINI di SUPERALCOLICI, AMARI o LIQUORI beve (es.: Whisky, Vodka, Brandy, Rhum, Gin, Cognac, Grappa, Amari, Sambuca)?

N. bicchierini al giorno _____ oppure N. bicchierini alla settimana _____ oppure N. bicchierini al mese _____ oppure Rara-mente ○ oppure Mai ○

Non scrivere qui.
Settimana Mese Anno
0 1 2 1 4 5 6 7 6 9
S 9 A 0 1 2 1 4 5 4 7 6 9

193 ▶ Quante LATTINE o BOTTIGLIETTE di BIRRA beve?

N. lattine al giorno _____ oppure N. lattine alla settimana _____ oppure N. lattine al mese _____ oppure Rara-mente ○ oppure Mai ○

Non scrivere qui.
Settimana Mese Anno
0 1 2 1 4 5 4 7 8 9
S 9 A 0 1 2 1 4 5 4 7 8 9

194 ▶ Quanti BICCHIERI di SUCCHI o SPREMUTE DI ARANCIO o POMPELMO beve?

N. bicchieri al giorno _____ oppure N. bicchieri alla settimana _____ oppure N. bicchieri al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana Mese Anno
0 1 2 1 4 5 4 7 6 9
S 9 A 0 1 2 1 4 5 4 7 8 9

195 ▶ Quanti BICCHIERI di SUCCHI DI FRUTTA beve (es.: Pera, Albicocca, Pesca, Mela)?

N. bicchieri al giorno _____ oppure N. bicchieri alla settimana _____ oppure N. bicchieri al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana Mese Anno
0 1 2 1 4 5 4 7 8 9
S 9 A 0 1 2 3 4 5 6 7 8 9

196 ▶ Quanti BICCHIERI di BIBITE ANALCOLICHE beve (es.: coca-cola, aranciate, chinotto, gazzose, ecc…)?

N. bicchieri al giorno _____ oppure N. bicchieri alla settimana _____ oppure N. bicchieri al mese _____ oppure Mai o quasi ○

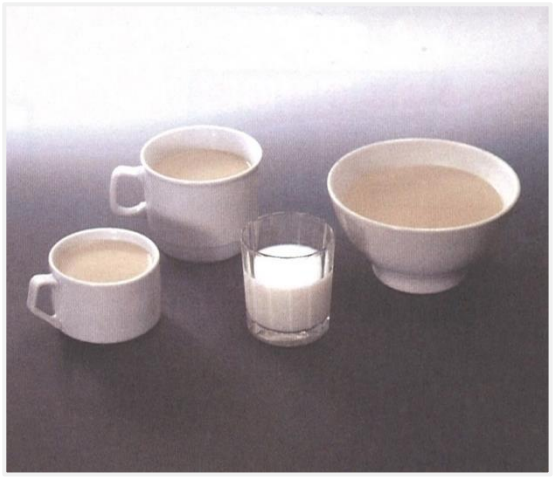
Non scrivere qui.
Settimana Mese Anno
0 1 2 1 4 5 4 7 8 9
S 9 A 0 1 2 1 4 5 4 7 8 9

CAFFÉ, LATTE E DOLCI

COME COMPILARE
COSI' ◉ NON COSI' ⊗

Nella foto ci sono una tazza piccola, una media, una grande e un bicchiere.

Pensi anche al consumo fuori pasto.



197 ▶ **Quanti bicchieri di LATTE BIANCO beve *(risponda pensando al bicchiere della foto)*?**

N. bicchieri al giorno _____	oppure	N. bicchieri alla settimana _____	oppure	N. bicchieri al mese _____	oppure	Mai o quasi ○

Non scrivere qui.
Settimana Mese Anno
S 9 A 0 1 2 1 4 5 6 7 6 9

198 ▶ **Quanti CAPPUCCINI (tipo Bar) beve?**

N. tazze al giorno _____	oppure	N. tazze alla settimana _____	oppure	N. tazze al mese _____	oppure	Mai o quasi ○

Non scrivere qui.
Settimana Mese Anno
S M A 0 1 2 1 4 5 4 7 8 9

199 ▶ **Quanti tazze di CAFFELATTE beve?**

N. tazze al giorno _____	oppure	N. tazze alla settimana _____	oppure	N. tazze al mese _____	oppure	Mai o quasi ○

Non scrivere qui.
Settimana Mese Anno
S 9 A 0 1 2 1 4 5 6 7 6 9

200 ▶ **Quando mangia CAFFELATTE che tazza usa? *(guardi la fotografia ed indichi la tazza usata annerendo un cerchietto)***

tazza piccola	tazza media	tazza grande
○	○	○

201 ▶ **Generalmente che tipo di LATTE consuma?**

intero	parzialmente scremato
○	○

202 ▶ **Quante tazzine di CAFFÉ beve?**

N. tazzine al giorno _____ oppure N. tazzine alla settimana _____ oppure N. tazzine al mese _____ oppure Mai o quasi ○

Non scrivere qui. Settimana S 9 Mese Anno A 0 1 2 1 4 5 4 7 8 9

Normalmente quando beve CAFFÈ in tazzina che tipo consuma?
(risponda in ogni riga annerendo un cerchietto):

	mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
203 ▶ - Caffè decaffeinato	○	○	○	○	○
204 ▶ - Caffè espresso tipo bar	○	○	○	○	○
205 ▶ - Caffè tipo moka	○	○	○	○	○
206 ▶ - Altri tipi	○	○	○	○	○

207 ▶ **Quante tazze di THÉ beve?**

N. tazze al giorno _____ oppure N. tazze alla settimana _____ oppure N. tazze al mese _____ oppure Mai o quasi ○

Non scrivere qui. Settimana S 9 Mese Anno A 0 1 2 1 4 5 4 7 6 9

208 ▶ **Quante volte mangia YOGURT?**

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui. Settimana S 9 Mese Anno A 0 1 2 1 4 5 4 7 8 9

209 ▶ **Generalmente che tipo di YOGURT consuma?**

intero	magro	alla frutta
○	○	○

210 ▶ **Quanti cucchiaini di ZUCCHERO mette nel *(indichi il numero di chicchiaini annerendo un cerchietto per ogni voce)*:**

		0	½	1	2	3	4	5 o più
- Latte	n°	○	○	○	○	○	○	○
- Caffelatte, Cappuccino	n°	○	○	○	○	○	○	○
- Caffè	n°	○	○	○	○	○	○	○
- Thè	n°	○	○	○	○	○	○	○
- Yogurt	n°	○	○	○	○	○	○	○
- Non uso mai zucchero		○						

211 ▶ **Quante FETTE BISCOTTATE mangia?**

N. fette al giorno _____ oppure N. fette alla settimana _____ oppure N. fette al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 A 0 1 2 1 4 5 4 7 6 9
Mese 0 1 2 1 4 5 4 7 8 9

212 ▶ **Quanti BISCOTTI tipo colazione mangia (biscotti secchi, wafer, ecc…)?**

N. biscotti al giorno _____ oppure N. biscotti alla settimana _____ oppure N. biscotti al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 A 0 1 2 3 4 5 6 7 8 9
Mese 0 1 2 1 4 5 4 7 8 9

213 ▶ **Quante BRIOCHES, CORNETTI o MERENDINE mangia?**

N. pezzi al giorno _____ oppure N. pezzi alla settimana _____ oppure N. pezzi al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 A 0 1 2 1 4 5 4 7 6 9
Mese 0 1 2 1 4 5 4 7 8 9

214 ▶ **Quante volte mangia MARMELLATA?**

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 A 0 1 2 1 4 5 6 7 6 9
Mese 0 1 2 1 4 5 4 7 8 9

215 ▶ **Quante volte mangia NUTELLA o altre CREME SPALMABILI?**

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S M A 0 1 2 1 4 5 4 7 8 9
Mese 0 1 2 1 4 5 4 7 8 9

216 ▶ **Quante volte mangia BURRO su pane o fette biscottate?**

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 A 0 1 2 1 4 5 4 7 6 9
Mese 0 1 2 1 4 5 6 7 6 9

217 ▶ **Quante volte mangia una porzione di DOLCE o PASTICCINI?**

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 A 0 1 2 1 4 5 4 7 8 9
Mese 0 1 2 1 4 5 4 7 8 9

Quando mangia una porzione di DOLCE o di PASTICCINI mangia
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
218	▶ - Torta farcita (al Cioccolato, Crema, Millefoglie, ecc…)	○	○	○	○	○
219	▶ - Torta non farcita (Margherita, Crostata, Panettone, Pandoro)	○	○	○	○	○
220	▶ - Dolce al cucchiaio (Tiramisù, Budino, Pannacotta)	○	○	○	○	○
221	▶ - Pasticceria secca	○	○	○	○	○
222	▶ - Paste ripiene (Bignè, Cannoli)	○	○	○	○	○

223 ▶ Quante volte mangia CIOCCOLATA (Tavolette, Cioccolatini)?

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 Anno A 0 1 2 1 4 5 6 7 6 9
Mese 0 1 2 1 4 5 4 7 8 9

224 ▶ Quanti pacchetti di CARAMELLE mangia?

N. pacchetti al giorno _____ oppure N. pacchetti alla settimana _____ oppure N. pacchetti al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 Anno A 0 1 2 1 4 5 4 7 8 9
Mese 0 1 2 1 4 5 4 7 8 9

225 ▶ Quante volte d'estate mangia un GELATO?

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 Anno A 0 1 2 1 4 5 4 7 6 9
Mese 0 1 2 1 4 5 4 7 8 9

226 ▶ Quante volte d'inverno mangia un GELATO?

N. volte al giorno _____ oppure N. volte alla settimana _____ oppure N. volte al mese _____ oppure Mai o quasi ○

Non scrivere qui.
Settimana S 9 Anno A 0 1 2 1 4 5 4 7 8 9
Mese 0 1 2 1 4 5 6 7 6 9

AROMI E SPEZIE

Ha l'abitudine di consumare alimenti con
(risponda in ogni riga annerendo un cerchietto):

		mai o quasi	qualche volta	spesso	molto spesso
227	▶ - Aglio	○	○	○	○
228	▶ - Peperoncino	○	○	○	○
229	▶ - Prezzemolo	○	○	○	○
230	▶ - Limone	○	○	○	○
231	▶ - Pepe	○	○	○	○
232	▶ - Soia	○	○	○	○

233 ▶ **Se consuma un pasto fuori casa, ha l'abitudine di aggiungere sale ai vari piatti?**

mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
○	○	○	○	○

La verdura fresca che Lei consuma abitualmente proviene da:

		mai o quasi	qualche volta	circa metà delle volte	il più delle volte	tutte le volte
234	▶ - NEGOZIO	○	○	○	○	○
235	▶ - MERCATO	○	○	○	○	○
236	▶ - SUPERMERCATO	○	○	○	○	○
237	▶ - NEGOZIO BIOLOGICO	○	○	○	○	○
238	▶ - PRODUZIONE PROPRIA (coltivata da Lei, Parenti o Amici)	○	○	○	○	○

239 ▶ **Possiede il surgelatore?**

SI	NO
○	○

In generale, quante volte al giorno mangia una porzione dei seguenti piatti? ***(risponda in ogni riga annerendo un cerchietto):***

		mai	meno di 1 volta al giorno	1 volta al giorno	tra 1 e 2 volte al giorno	2 volte al giorno	più di 2 volte al giorno
240	▶ - Primi piatti	○	○	○	○	○	○
241	▶ - Carne	○	○	○	○	○	○
242	▶ - Verdura cruda	○	○	○	○	○	○
243	▶ - Verdura cotta	○	○	○	○	○	○
244	▶ - Frutta fresca	○	○	○	○	○	○

MODALITÀ DI COTTURA

COME COMPILARE
COSI' ◉ NON COSI' ⊗

Normalmente che TIPI DI GRASSI usa in casa sua? ***(risponda in ogni riga annerendo uno o più cerchietti):***

		non so	burro	margarina	olio di oliva	olio di semi
245	▶ - Per cucinare in umido o arrosto	○	○	○	○	○
246	▶ - Per friggere	○	○	○	○	○

247 ▶ **Se usa olio di semi, indichi il tipo di semi**

non so	arachidi	girasole	mais	soia	altri semi
○	○	○	○	○	○

248 ▶ **C'è qualche ALIMENTO o PIATTO che mangia almeno una volta al mese e che non è considerato in questo questionario?**

SI	NO
○	○

descriva liberamente

_____

_____

_____