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Review

Environmental and lifestyle risk factors for early-onset dementia: a systematic review

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Abstract. *Background and aim:* The term early-onset dementia (EOD) encompasses several forms of neurodegenerative diseases characterized by symptom onset before 65 years and leading to severe impact on subjects already in working activities, as well as on their family and caregivers. Despite the increasing incidence, the etiology is still unknown, with possible association of environmental factors, although the evidence is still scarce. In this review, we aimed to assess how several environmental and lifestyle factors may be associated with the onset of this disease. *Methods:* We conducted a literature search in PubMed and EMBASE databases up to May 6, 2022, to retrieve epidemiological studies evaluating the effect of environmental and lifestyle factors on EOD risk. *Results:* We eventually included 22 studies, ten with cohort and twelve with case-control design. Traumatic injury, especially on the head/brain, some cardiovascular diseases such as atrial fibrillation and stroke, metabolic diseases including diabetes and hypercholesterolemia, and alcohol consumption have been identified as potential risk factors for EOD. Conversely, playing leisure activities including sports (without trauma), higher educational attainment and higher adherence to Mediterranean DASH-Intervention for Neurodegenerative Delay (MIND) diet appeared to be protective for EOD. *Conclusions:* The literature on environmental risk factors for EOD has been considerably growing in recent years. Overall, it supports an association between some environmental and lifestyle factors with disease risk. However, additional high-quality research is required to confirm these relations and its causal nature (www.actabiomedica.it).

Key words: Early-onset dementia; environment; lifestyle; prevention; risk factors.

Introduction

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) defines dementia as a group of disorders characterized by the development of multiple cognitive deficits including memory loss and dysfunction in at least another cognitive domain (executive function, language, praxis, and gnosis), severe enough to interfere with daily living activities (1).

When the onset of symptoms occurs before 65 years, we talk about early-onset dementia (EOD) (2), also known as Young Onset Dementia (YOD), in contrast to Late Onset Dementia (LOD) with symptom onset ≥ 65 years (3). Recent population studies showed that EOD prevalence in people aged 30-64 years was 54.0 to 76.3 per 100,000 inhabitants, increasing from 98.1 to 163.0 per 100,000 inhabitants for those aged 45-64 years (4-6), while incidence was 13.2 per

100,000 inhabitants/year in subjects aged 30-64 years (4). EOD, in particular, is a devastating condition due to its chronic, progressive and irreversible course affecting subjects still in working age (6); furthermore, EOD has a significant impact on family members and caregivers (7,8).

The most common EOD form is Alzheimer's dementia (EOAD), followed by vascular dementia (VaD), frontotemporal dementia (EOFTD), alcohol-related dementia and other conditions that occur secondarily to other diseases, including Parkinson's disease, Huntington's disease, Down's syndrome, multiple sclerosis or human immunodeficiency virus (HIV) infection (4,9,10).

Genetic risk factors may play an important role in EOD etiology, such as *APP*, *PSEN1/2* gene mutations in EOAD, and *MAPT*, *GNR* and *C9ORF72* in EOFTD (11). However, only a minority of EOD cases has a genetic inheritance as a clear cause (12,13), and in recent years the interest in the potential environmental risk factors of dementia has considerably increased (14-17), and particularly for EOD, as shown by a recent systematic review that identified 14 studies on EOD etiology (12). Several additional epidemiological studies have become available since this last review, providing interesting findings and potential clue to the environmental etiology of this disease, possibly in the context of an interaction between environmental and genetic factors. For these reasons, we aimed at systematically reviewing the studies that addressed the environmental risk factors for EOD.

Methods

We searched of the PubMed and EMBASE literature databases through May 6, 2022. In PubMed, we entered the search string "(risk factor*) AND (early-onset dementia)", using language (English) and participants (human) restrictions. In EMBASE we used the string "('dementia'/exp/mj OR 'amentia' OR 'dementia' OR 'demention') AND 'early-onset' AND ('risk factor'/exp/mj OR 'relative risk' OR 'risk factor' OR 'risk factors')". Looking at titles and abstracts of the retrieved studies we selected those potentially suitable for this review after full-text evaluation, according to the following criteria: a) the study had a cohort or case-control design and included participants affected by EOD; b) addressed an environmental (including lifestyle) risk factor; c) quantified the impact of these factors on EOD (symptom onset < 65 years); d) used validated diagnostic criteria for dementia, and e) included a comparison group, consisting either of control subjects or LOD cases. All-cause early-onset dementias were included and risk factors were considered irrespective of a specific dementia diagnosis.

We extracted the following data from each study: study design, setting, sample size, risks factors, ascertainment of exposure, exposure period, age of onset, the confounders for which the multivariable analysis was adjusted for (if any), and the risk estimates (e.g. odds ratio-OR, risk ratio-RR or hazard ratio-HR) along with their 95% confidence intervals (CI). Maximally adjusted results are presented with the aim of reducing the risk of residual confounding.

Results

We first identified 1921 hits in literature search, as shown in the PRISMA 2020 flowchart (Figure 1). We then discarded most of these records according to the inclusion criteria and based on title and abstract screening. The full-text of the 22 studies that appeared to be suitable for our review was analyzed, their main characteristics being shown in Tables 1 and 2. Ten were cohort studies (Table 1), twelve case-control (Table 2). The cohort studies were published between 2010 and 2021, six were carried out in Europe, three in Asia and one in North America (18-27), while case-control studies were published between 1991 and 2022, five in Europe, four in North America, two in Asia and one in Oceania (28-39).

The maximally adjusted risk estimates grouped by putative risk or protective factors extracted from these studies are shown in Tables 3-7.

One retrospective cohort study found a strong association between traumatic brain injury (TBI) and all-cause EOD (HR 5.49, 95% CI 4.97-6.06). The association was stronger in men with the lowest cognitive test scores or education (26). Similarly, increase

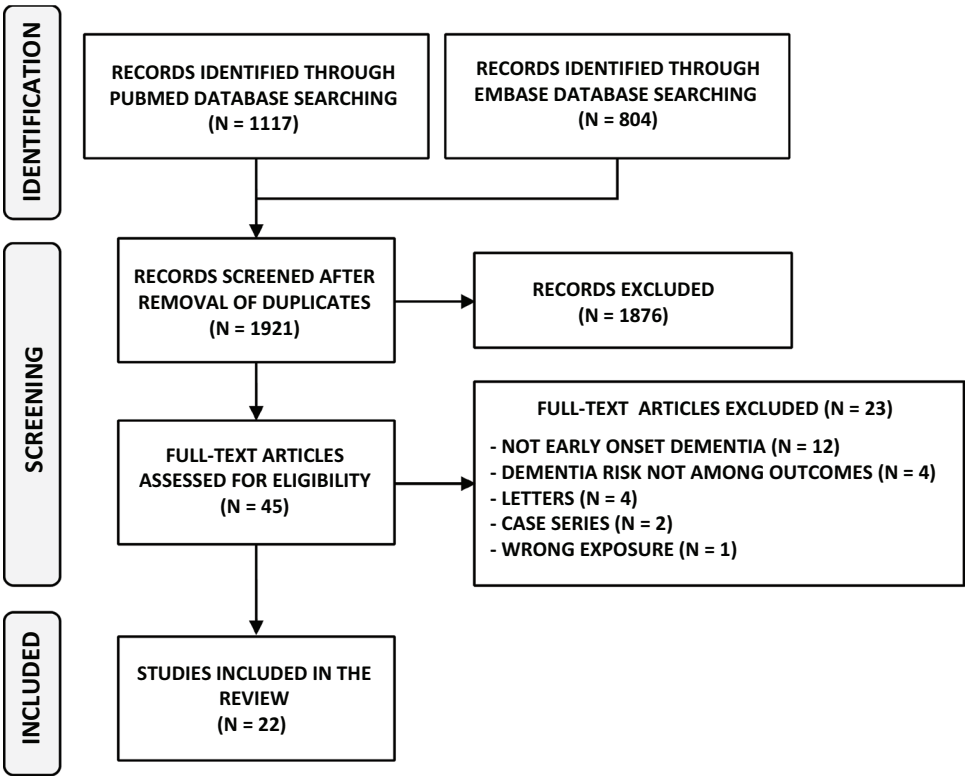

Figure 1. Flow-chart describing the process of study selection.

Table 1. Characteristics of the included studies with cohort design.

Author and year	Country	N (EOD cases)	Mean age (SD or range)	Risk factors	Ascertainment of exposure	Exposure period	Adjustments
Bagge 2018 (18)†	Denmark	10,632 and 103,403 (33 and 145)	n/r (30-80+)	Congenital Heart Diseases (CHD)	Medical record review	Any time before 30 years	Sex, birth year
Basit 2018 (19)	Denmark	1,178,005 (1225)	58.5	History of pre-eclampsia	Data from the DNPR	23 years (1994-2017)	Diabetes, hypertension, cardiovascular disease
Han 2020 (20)	South Korea	6,595,271 (19,915)	76.5	Diabetes mellitus, NAFLD, γ-GT	Data from Korean NHIS-HEALS database	7 years (2009-2015)	Sex, age, clinical variables
Kim 2020 (21)	South Korea	428,262 (1112)	61.7 (9.9); 55.5 (9.1)‡	Atrial Fibrillation (AF)	Data from Korean NHIS-HEALS database	9 years (2005-2013)	Sex, age, clinical variables, cardiovascular medications

Table 1 (*Continued*)

Author and year	Country	N (EOD cases)	Mean age (SD or range)	Risk factors	Ascertainment of exposure	Exposure period	Adjustments
Liao 2015 (22)	Taiwan	665,330 (n/r)	61.7 (9.9)	Atrial fibrillation (AF)	Data from the NHIRD database	16 years (1996-2011)	Sex, age, clinical variables, cardiovascular medications, income level and Charlson index
Mahmoudi 2021 (23)	United States	923 535 (7019)	45+	Traumatic Spinal Cord Injury (TSCI)	Data from OCDM database	10 years (2007-2017)	Age, sex, ethnicity, cardiometabolic, psychological, musculoskeletal chronic conditions, US Census division, socioeconomic variables
Nordstrom 2013 (24)	Sweden	488,484 (487)	54.6 (4.5)	Education, intelligence, childhood development, blood pressure, cardiovascular illness, BMI, psychiatric illness, alcohol, other drugs	Health record	37 years (range 0-41 years)	Age, weight, family history of dementia
Nyberg 2014 (25)[§]	Sweden	824,500 and 823,207 (657 and 662)	n/r (18-60)	Cognitive performances, cardiovascular fitness	Physical and neuropsychological testing	From age 18	Calendar year, BMI, region, conscription test center; parental education
Osler 2020 (26)	Denmark	658,447 (4164)	n/r	TBI, alcohol abuse, depression, education, cognitive ability	Data from the DNPR	40 years (1977-2016)	Fractures, cognitive ability, education, psychiatric comorbidity, alcohol, depression
Phung 2010 (27)	Denmark	2,313,388 (355)	n/r (40-80+)	Hysterectomy, unilateral and bilateral oophorectomy	Data from the DNPR	From age 40	Calendar period, age at dementia diagnosis

Footnotes: [†]CHD cohort and general population cohort respectively; [‡]No AF and Incident AF respectively; [§]Sample taken by the same population; **Abbreviations:** AF: Atrial Fibrillation; BMI: Body Mass Index; DNPR: Danish National Patient Register; γ-GT: Gamma Glutamyltransferase; NHIRD: National Health Insurance Research Database; NHIS-HEALS: Korea National Health Insurance Service-Health Screening; n/r: not reported; OCDM: Optum Clinformatics Data Mart; NAFLD: Non-Alcoholic Fatty Liver Disease; SD: Standard Deviation; TBI: Traumatic Brain Injury; TSCI: Traumatic Spinal Cord Injury.

risk was reported for traumatic spinal cord injury (HR 1.93, 95% CI 1.06-3.51) (23). Two case-control studies found a positive relation between TBI and EOD (OR 1.75, 95% CI 1.47-2.07) (35), particularly for EOFTD (OR 5.96, 95% CI 3.96-8.99) (34). A recent case-control study found no relation with any trauma that needed medical evaluation (OR 0.93, 95% CI 0.42-2.07) (28).

Table 2. Characteristics of the included studies with case-control design.

Author and year	Country	N Cases/ controls	Onset age (SD or range)	Risk factors	Assessment of exposure	Exposure period	Adjustments
Adani 2020 (28)	Italy	58/54	59.3 (4.7)	Marital status, occupational exposure to toxic agents, trauma, leisure activities, sports, selenium, smoking	Anamnestic questionnaire	Any time	Sex, age, educational attainment
Cations 2018 (29)	Australia	96/175	56.9 (5.0)	Low-lifetime cognitive leisure activity, stroke or Transient Ischemic Attack (TIA), distal hypertension, proximal depression, alcohol use disorders	Retrospective self or proxy report		Age, sex, race, family history of dementia
Chen 2017 (30)	France	102/306	59.5 (3.8)	Education, alcohol, smoking, BMI, systolic BP, BP-lowering medication, hypercholesterolemia, hypertrigliceridemia, lipid-lowering medication, diabetes mellitus	Data collected by a first visit	5 years	Age, sex, educational level
Cheng 2021 (31)	Taiwan	1308/1308	59.64 (6.49)	Prior tinnitus	Data from Taiwan NHIRD	Any time before 2010	Age, income, geographical location, urbanization level, hypertension, diabetes, coronary heart disease, dyslipidemia, obesity, hearing loss, alcohol abuse
Filippini 2020 (32)	Italy	54/54	59.8 (45-65)	GM diet, DASH diet, MIND diet	FFQ	Any time before symptom onset	Sex, educational attainment, marital status
Kadohara 2017 (33)	Japan	371/1484	56.3 (5.3)	Diabetes mellitus, co-prescribed drugs	Data from JMDC database	12 years (2005-2016)	Age, sex, type of hospital
Kennedy 2022 (34) (31)	United States	973/973	54 (2.4)	Any severity TBI, epilepsy, other neurological diagnoses, cardiac disease	Data from VA and DoD health systems	17 years	Sociodemographic conditions, medical comorbidities
Mendez 2015 (35)	United States	1449/1449	57.3 (5.7)	TBI with LOC	Data from NACC-database EOAD group	Any time	Sex, age, race, years of education

Table 2 (*Continued*)

Author and year	Country	N Cases/ controls	Onset age (SD or range)	Risk factors	Assessment of exposure	Exposure period	Adjustments
Slooter 1999 (36)	The Netherlands	109/119	57.9 (6.4)	Estrogen	Retrospective self or proxy report	Any time before symptom onset	Age, education
van Duijn 1991 (37)	The Netherlands	122/146	Men: 56.3 (6.0) Women: 57.1 (4.0)	Smoking	Retrospective proxy report	Any time before symptom onset	Sex, age, residence, cardiovascular diseases, alcohol
Vivanti 2021 (38)	United States	445,386/ 798,828	30-64	ASD only, ASD with ID, ID only	Data from MAX	5 years	Sex, age, race, urbanicity, poverty status, depression, other mental disorders, cardiovascular risk factors
Willer 2018 (39)	United States	21/21	n/r (36-72)	Former contact-sport	Retrospective proxy report	2 or more seasons	Education

Abbreviations: ASD: Autism Spectrum Disorder; BP: Blood Pressure; DASH: Dietary Approaches to Stop Hypertension; DoD: Department of Defense; FFQ: Food Frequency Questionnaire; GM: Greek-Mediterranean; ID: Intellectual Disability; JMDC: Japan Medical Data Center;; MAX: Medicaid Analytic eXtract; MIND: Mediterranean DASH-Intervention for Neurodegenerative Delay; NACC: National Alzheimer's Coordinating Center; NHIRD: Taiwan National Health Insurance Research Database; SD: Standard Deviation; TIA: Transient Ischemic Attack; VA: Veterans Administration;

Table 3. Traumatic factors and risk of early-onset dementia.

Author and year	Comparison groups	OR, HR or RR (95% CI)	Type of EOD
Mahmoudi 2021 (23)	TSCI (vs no)	1.93 (1.06-3.51)	AD
Osler 2020 (26)	TBI during follow up (vs no TBI) Fractures (unspecified site) (vs no)	5.49 (4.97-6.06) 1.92 (1.78-2.06)	All types
Adani 2020 (28)	Any trauma requiring medical evaluation Head trauma Upper arm trauma Lower arm trauma Electric shock/trauma	0.93 (0.42-2.07) 1.54 (0.47-4.99) 1.38 (0.47-4.03) 0.85 (0.34-2.13) 0.18 (0.01-2.22)	AD and FTD
Kennedy 2022 (34)	Any severity TBI	2.26 (1.59-3.21) 5.96 (3.96-8.99)	AD and FTD
Mendez 2015 (35)	TBI with LOC (vs no TBI)	1.75 (1.47-2.07)	AD

Abbreviations: AD: Alzheimer's Dementia; CI: Confidence Interval; FTD: Frontotemporal Dementia; HR: Hazard Ratio; LOC: Loss of Consciousness; OR: Odds Ratio; RR: Relative Risk; TBI: Traumatic Brain Injury; TSCI: Traumatic Spinal Cord Injury.

Two studies found a lower risk for EOD in smokers compared to never smokers (30,37), a third study found an unclear association, as well as for exposure to passive smoke (OR 1.17, 95% CI 0.47-2.88) (28). A Japanese case-control study identified an increased risk for EOD for diabetes mellitus in men (OR 1.68, 95% CI 1.06-2.67) (33), while a Korean cohort study found a positive association for diabetes mellitus

Table 4. Cardiovascular and cerebrovascular factors and risk of early-onset dementia.

Author and year	Comparison groups	OR, HR or RR (95% CI)	Type of EOD
Bagge 2018 (18)	CHD (vs general population cohort)	2.59 (1.76-3.81)	All types
Basit 2018 (19)	History of pre-eclampsia (vs no history) History of pre-eclampsia (vs no history) History of pre-eclampsia (vs no history) History of pre-eclampsia (vs no history)	1.10 (0.87-1.40) 1.41 (0.64-3.10) 1.08 (0.68-1.72) 1.13 (0.84-1.52)	All types; VaD; AD; Other/unspecified
Han 2020 (20)	IFG (vs normoglycemia) Incident diabetes (vs normoglycemia) Prevalent diabetes (vs normoglycemia) NAFLD + (vs NAFLD -) γ-GT Q2 (vs Q1) γ-GT Q3 (vs Q1) γ-GT Q4 (vs Q1)	1.04 (1.00-1.07) 1.21 (1.12-1.30) 1.73 (1.66-1.81) 1.02 (0.98-1.06) 1.00 (0.96-1.04) 1.01 (0.97-1.06) 1.22 (1.17-1.27)	All types
Kim 2020 (21)	Incident AF (vs no AF)	2.91 (1.93-4.41)	All types
Liao 2015 (22)	AF (vs no AF)	1.43 (1.31-1.56)	All types
Nordstrom 2013 (24)	High systolic blood pressure age 18 Myocardial infarction any time age 18 to diagnosis (vs no myocardial infarction) Stroke any time age 18 to diagnosis (vs no stroke) High weight age 18	0.90 (0.82-0.99) 0.99 (0.61-1.59) 2.96 (2.02–4.35) 0.95 (0.85–1.07)	All types
Nyberg 2014 (25)	Medium cardiovascular fitness age 18-60 years Medium cardiovascular fitness age 38-60 years Low cardiovascular fitness age 18-60 years Medium cardiovascular fitness age 38-60 years (all vs high fitness)	1.28 (1.08–1.53) 1.59 (1.26–2.02) 1.92 (1.43–2.58) 2.10 (1.36–3.24)	All types
Adani 2020 (28)	Ever smoking Current smoking Passive smoking exposure	1.28 (0.58-2.86) 1.01 (0.37-2.79) 1.17 (0.47-2.88)	AD and FTD
Cations 2018 (29)	Stroke or TIA (vs no) Distal hypertension (>10 years from dementia onset)	9.92 (2.24-44.0) 2.55 (1.33-4.73)	All types
Chen 2017 (30)	Former smoking (vs never) Current smoking (vs never) BMI Systolic blood pressure Hypercholesterolemia (vs no) Hypertriglyceridemia (vs no) Diabetes mellitus (vs no)	1.25 (0.62-2.52) 0.42 (0.15-1.17) 0.90 (0.85-0.95) 0.98 (0.96-0.99) 2.03 (0.96-4.32) 0.33 (0.11-0.98) 2.35 (0.57-9.66)	AD
Kadohara 2017 (33)	Diabetes mellitus (vs no diabetes mellitus) - All Men Women	1.31 (0.90-1.92) 1.68 (1.06-2.67) 0.73 (0.38-1.39)	AD
Kennedy 2022 (34)	Cardiac diseases	1.36 (1.10-1.67)	AD and FTD
van Duijn 1991 (37)	1–10 daily cigarettes (vs never smoked) 11–20 daily cigarettes (vs never smoked) >20 daily cigarettes (vs never smoked)	0.81 (0.44–1.49) 0.67 (0.34-1.32) 0.26 (0.11-0.61)	AD

Abbreviations: AD: Alzheimer's Dementia; AF: Atrial Fibrillation; BMI: Body Mass Index; CHD: Congenital Heart Disease; CI: Confidence Interval; FTD: Frontotemporal Dementia; γ-GT: Gamma Glutamyltransferase; HR: Hazard Ratio; OR: Odds Ratio; Q: Quartile; RR: Relative Risk; TIA: Transient Ischemic Attack; VaD: Vascular Dementia.

Table 5. Association between Medications, substance abuse and estrogen-related factors and early-onset dementia risk.

Author and year	Comparison groups	OR, HR or RR (95% CI)	Type of EOD
Han 2020 (20)	Diabetes treatment maintenance (vs normoglycemia) Diabetes treatment failure (vs normoglycemia)	1.54 (1.52-1.55) 1.68 (1.64-1.73)	All types
Nordström 2013 (24)	Antidiabetics medications use any time age 18 (vs no use) Neuroleptics medications use any time age 18 (vs no use) Use of antidepressants (vs no use) Alcohol intoxication (vs no) Other drugs intoxication (vs no)	0.77 (0.55-1.09) 2.75 (2.09-3.60) 1.89 (1.53-2.34) 4.82 (3.83-6.05) 1.54 (1.06-2.24)	All types
Osler 2020 (26)	Alcohol abuse	3.87 (3.22-4.66)	All types
Phung 2010 (27)	Hysterectomy and bilateral oophorectomy (vs no) 40–49 years 50–59 years Hysterectomy and unilateral oophorectomy (vs no) 40–49 years 50–59 years Hysterectomy only (vs no) 40–49 years 50–59 years Bilateral oophorectomy only (vs no) 40–49 years 50–59 years Unilateral oophorectomy only (vs no) 40–49 years 50–59 years	 2.33 (1.44-3.77) 1.27 (1.01-1.60) 2.10 (1.28-3.45) 0.88 (0.61-1.26) 1.38 (1.07-1.78) 0.89 (0.76-1.05) 2.36 (0.76-7.34) 0.75 (0.31-1.80) 1.18 (0.71-1.69) 1.08 (0.78-1.50)	All types
Cations 2018 (29)	Heavy alcohol use	3.53 (0.94-13.30)	All types
Chen 2017 (30)	Regular alcohol consumption (vs no) BP-lowering medication (vs no) Lipid-lowering medication (vs no)	0.08 (0.02-0.28) 1.93 (1.06-3.51) 0.72 (0.31-1.68)	AD
Kadohara 2017 (33)	Antidepressants (vs none) Antipsychotics (vs none) Antithrombotics (vs none) Antihypertensives (vs none) Antihyperlipidemics (vs none) Polypharmacy (≥5 drugs) (vs 0-4 drugs)	9.88 (6.57-14.87) 5.57 (4.21-7.37) 2.77 (1.97-3.89) 1.24 (0.96-1.59) 1.18 (0.89-1.57) 2.87 (2.21-3.73)	AD
Slooter 1999 (36)	Exogenous estrogen use (vs no use)	0.34 (0.12-0.94)	AD

Abbreviations: AD: Alzheimer's Dementia; BP: Blood Pressure; CI: Confidence Interval; HR: Hazard Ratio; OR: Odds ratio; RR: Relative Risk.

(HR 1.21, 95% CI 1.12-1.30) and impaired fasting glucose (HR 1.04, 95% CI 1.00-1.07), especially in patients who presented the highest quartile in the gamma-glutamiltransferase value (HR 1.22, 95% CI 1.17-1.27) (20). Two studies found a lower risk for high systolic blood pressure (24,30), but distal hypertension (i.e. >10 years from dementia onset) appears to be a significant risk factor (OR 2.55, 95% CI 1.33-4.73) (29). Hypercholesterolemia had a positive association with EOD (OR 2.03, 95% CI 0.96-4.32), while hypertriglyceridemia was inversely associated (OR 0.33, 95% CI 0.11-0.98) (30). A cohort studies showed an increased risk for all-cause EOD for both medium (HR 1.28, 95% CI 1.08-1.53) and low (HR 1.92, 95% CI 1.43-2.58) cardiovascular fitness at age 18 (25). As regards atrial fibrillation, two cohort studies reported an increased EOD risk with HRs of 3.81 (95% CI 2.75-5.29) (21) and 1.43 (95% CI 1.31-1.56) (22). Similarly, one cohort and one case-control study showed increased risk of congenital heart diseases (HR 2.59, 95% CI 1.76-3.81) (18), and cardiac diseases such as cardiac arrhythmia, congestive heart

Table 6. Education and neuropsychiatric illness and early-onset dementia risk.

Author and year	Comparison groups	OR, HR or RR (95% CI)	Type of EOD
Nordström 2013 (24)	≤ Elementary school (vs > elementary school) Low performance cognitive tests age 18 (vs high) Depression (vs no)	1.02 (0.83-1.25) 1.26 (1.14-1.40) 1.89 (1.53-2.34)	All types
Nyberg 2014 (25)	Medium performance on cognitive tests age 18-60 years Medium performance on cognitive tests age 38-60 years Low performance on cognitive tests age 18-60 years Low performance on cognitive tests age 38-60 years (all vs high performance)	 1.72 (1.35-2.20) 2.26 (1.57-3.24) 3.82 (2.96-4.93) 4.92 (3.38-7.14)	All types
Osler 2020 (26)	Cognitive ability, middle tertile (vs low) Cognitive ability, high tertile (vs low) Middle education (vs low) High education (vs low) Depression	0.68 (0.63-0.73) 0.51 (0.46-0.56) 0.98 (0.90-1.04) 0.88 (0.77-1.00) 1.87 (1.39-2.80)	All types
Adani 2020 (28)	High school or more (vs middle school or less)	0.43 (0.20-0.94)	AD and FTD
Cations 2018 (29)	High education, high complexity occupation (ref) High education, low complexity occupation Low education, high complexity occupation Low education, low complexity occupation Proximal depression Low lifetime cognitive leisure activities (vs high)	 1.70 (0.75–3.88) 3.24 (1.38–7.63) 5.85 (1.93–17.80) 3.71 (1.63-8.46) 3.48 (1.46-8.33)	All types
Chen 2017 (30)	High educational level (vs low)	0.82 (0.75-0.89)	AD
Cheng 2021 (31)	Prior tinnitus (vs no)	1.628 (1.321-2.006)	All types
Kennedy 2022 (34)	Epilepsy (vs no) Other neurological diagnoses (vs no)	4.80 (3.30-6.97) 2.00 (1.35-2.97)	AD and FTD
Vivanti 2021 (38)	No ASD nor ID diagnosis (ref) ASD only ASD and co-occurring ID ID only	 1.96 (1.69-2.28) 2.89 (2.62-3.17) 3.01 (2.87-3.15)	All types

Abbreviations: AD: Alzheimer's Dementia; ASD: Autism Spectrum Disorder; CI: Confidence Interval; FTD: Frontotemporal Dementia; HR: Hazard Ratio; ID: Intellectual Disability; OR: Odds Ratio; RR: Relative Risk.

failure and valvular heart disease (OR 1.36, 95% CI 1.10-1.67) (34). One retrospective cohort study found a strong positive association between early-onset vascular dementia and pre-eclampsia, but after adjustments the correlation was weaker (HR 1.41, 95% CI 0.64-3.10) (19). A strong association between EOD and cerebrovascular disease, namely stroke (HR 2.96, 95% CI 2.02-4.35) and transient ischemic attack (OR 9.92, 95% CI 2.24-44.0), emerged in the two studies that assessed these factors (24,29).

One case-control study and two retrospective cohort studies reported that heavy drinking, alcohol abuse and alcohol intoxication were positively associated with EOD risk (24,26,29). Antidiabetics and cardiovascular medications were inconsistently associated with EOD risk (24,30,33), though a positive correlation for diabetes treatment failure was found in one cohort study (HR 1.68, 95% CI 1.64-1.73) (20). A strong positive association was found with antidepressant (HR 1.89, 95% CI 1.53-2.34), neuroleptic (HR 2.75, 95% CI 2.09-3.60) and antipsychotic drugs (OR 5.57, 95% CI 4.21-7.37), as well as polypharmacy (OR 2.87, 95% CI 2.21-3.73) (33) and drug intoxication, with OR ranging from 1.06 to 2.24 (24). One case-control study reported an inverse association between estrogen use and EOD in menopausal women (OR 0.34, 95% CI 0.12-0.94) (36), while a retrospective cohort study found an increased EOD risk for hysterectomy (HR 1.38, 95% CI 1.07-1.78), while there was no similar effect from oophorectomy (27).

Table 7. Childhood development, lifestyles and exposures and early-onset dementia risk.

Author and year	Comparison groups	OR, HR or RR (95% CI)	Type of EOD
Nordström 2013 (24)	Knee muscle strength	1.02 (0.92-1.12)	All types
Adani 2020 (28)	Single/separated/widowed (vs married/unmarried) Occupational exposure to lead Occupational exposure to mercury Occupational exposure to selenium Occupational exposure to aluminum Occupational exposure to pesticides Occupational exposure to solvents and dyes Playing sports Dietary suppl. containing selenium past 20 years	1.78 (0.56-5.59) 0.83 (0.22-3.15) 0.31 (0.02-4.01) 1.56 (0.09-27.77) 2.59 (0.43-15.66) 2.28 (0.67-7.77) 1.74 (0.61-5.02) 0.36 (0.15-0.89) 2.50 (0.89-7.02)	AD and FTD
Filippini 2020 (32)	GM diet (3rd vs 1st tertile) DASH diet (3rd vs 1st tertile) MIND diet (3rd vs 1st tertile)	0.45 (0.16-1.26) 0.60 (0.21-1.72) 0.31 (0.11-0.90)	AD and FTD
Willer 2018 (39)	Former contact-sport athletes (vs non-contact-sport athletes)	Slight increase MCI	All types

Abbreviations: AD: Alzheimer's Dementia; CI: Confidence Interval; DASH: Dietary Approaches to Stop Hypertension; FTD: Frontotemporal Dementia; GM: Greek-Mediterranean; HR: Hazard Ratio; MCI: mild cognitive impairment; MIND: Mediterranean DASH-Intervention for Neurodegenerative Delay; OR: Odds Ratio; RR: Relative Risk.

Six studies found an inverse association between EOD and the neuropsychological and cognitive function as assessed through cognitive performance tests and cognitive leisure activities (24-26,28-30). Of these, two retrospective cohort studies investigating the same population found that lower performance on cognitive tests at age 18 conferred an increased risk towards any EOD, whether measured continuously (HR 1.26, 95% CI 1.14-1.40) (24) or categorically (HR 3.82, 95% CI 2.96-4.93) (25). Three studies investigated the association between depression and EOD, in all cases finding a positive association (24,26,29). Two recent case-control studies found a relation between EOD and tinnitus (OR 1.63, 95% CI 1.32-2.01) (31), epilepsy (OR 4.80, 95% CI 3.30-6.97) and other neurological disorders (OR 2.00, 95% CI 1.35-2.97) (34), finding a positive association.

About a possible role of diet, three well-known healthy dietary patterns, namely the Greek-Mediterranean (GM) diet (OR 0.84, 95% CI 0.65-1.09), the Dietary Approaches to Stop Hypertension (DASH) diet (OR 0.98, 95% CI 0.90-1.06) and the Mediterranean DASH-Intervention for Neurodegenerative Delay (MIND) diet (OR 0.66, 95% CI 0.47-0.91), were inversely associated with EOD risk in an Italian population (32).

A possible protective role of general sport practice was found in a case-control study (OR 0.36, 95% CI 0.15-0.89) (28), while former contact sport players could undergo a slightly increased risk of mild cognitive impairment (39). An Italian case-control study found a slightly increased EOD risk for herbicide use during gardening (OR 1.31, 95% CI 0.28-6.08), a strong relation for occupational exposure to chemicals, especially pesticides (OR 2.28, 95% CI 0.67-7.77) and fertilizers (OR 1.96, 95% CI 0.39-9.74), null results for magnetic field exposure (OR 0.37, 95% CI 0.04-3.81), an increased risk for occupational exposure to aluminum (OR 2.59, 95% CI 0.43-15.66), as well as for long-term use of selenium-containing dietary supplements (OR 2.50, 95% CI 0.89-7.02) (28).

Discussion

Overall, the studies included in this review suggest that some modifiable factors, both environmental and linked to lifestyle, increase the risk of EOD. However, we found some inconsistencies across studies, some methodological limitations hamper the reliability of their findings, and the overall number of studies is still limited.

In particular, the evidence collected highlights a possible causal role of traumatic brain injury (TBI) in EOD etiology. Previous studies investigating the association between head trauma and risk of dementia generally indicated that TBI produces chronic and progressive neurodegenerative changes leading to late neurologic dysfunction (40,41). Despite the mechanisms underpinning this association are still unclear, it seems that microglial activation persists many years after the initial brain trauma has been observed (42). In addition, a systematic review and meta-analysis of 32 observational studies showed that head injury significantly increased the risk of any dementia (RR 1.63, 95% CI 1.34-1.99) and in particular AD (RR 1.51, 95% CI 1.26-1.80) (43).

As regards sport trauma, it has been known since almost a century that professional boxers, after or at the end of their career, may develop a progressive neurological disorder called 'punch drunk syndrome' (44). After the recognition of similar types of pathology also in football players (45,46) and other contact sport athletes (47), as well as in soldiers exposed to explosive blasts (48), both research interest and public awareness of this association have increased dramatically (49). As a matter of fact, this condition of degenerative neuropathology has been subsequently moved into the more general term of chronic traumatic encephalopathy. At the same time, epidemiological data provide increasing support for an association between previous TBI and future dementia in people aged > 50 years (50,51), with lower risk in individuals with mild TBI, and higher risk in those with repeated TBIs (52).

Besides the positive association of trauma and some contact sports with EOD, our review suggests an overall inverse association between physical activity and risk of EOD, in line with findings concerning late-onset dementia (53-58). As possible underlying mechanisms, physical activity and sport practice in general have been associated to decreased insulin resistance and improved profile of metabolic risk factors (59). Moreover, a recent review suggested a positive association between atrial fibrillation and risk of EOD using 70 years-old as cutpoint (60) with possible mechanisms related to cerebral hypoperfusion and altered blood flow inducing brain atrophy (61,62).

Occupational exposure to various agents seems to play a detrimental effect for EOD onset, including several chemicals and pesticides. In particular, several studies suggest long-term cognitive effects of chronic exposure to pesticides and raise the issue of the risk of evolution towards dementia and other neurodegenerative diseases (63,64). A recent systematic review regarding occupational exposure and neurodegenerative diseases reported that occupational exposure to pesticides brings about at least 50% increased risk for a neurodegenerative disease (65). In addition, some evidence for an increased risk of EOD due to occupational exposure to heavy metals and trace elements has been also found: overexposure to trace elements including high chronic aluminum exposure has been related to increased risk for neurodegenerative diseases, including Alzheimer's dementia, Parkinson's disease, and amyotrophic lateral sclerosis (66-68). As regards selenium, in a review on selenium and Alzheimer's disease (69) two studies reported a negative correlation between selenium levels in water and cognitive performances in two cohorts of elderly Chinese subjects. Similarly, in an Italian cohort study assessing levels of selenium species in cerebrospinal fluid (CSF), it has been shown that higher amounts of inorganic selenium may predict conversion from mild cognitive impairment to Alzheimer's dementia (70).

Another lifestyle factor found to be associated with EOD risk in this review is heavy alcohol consumption. Ethanol and its metabolite acetaldehyde have a direct neurotoxic effect. Additionally, high alcohol intake tends to be associated with higher prevalence of cardiovascular risk factors, psychiatric illnesses and several conditions which can adversely affect the brain, such as epilepsy, history of head trauma and hepatic encephalopathy (31).

A large number of studies has identified high educational attainment, high cognitive fitness and ability, and high cognitive leisure activities, as beneficial factors for EOD risk, in line with what has been observed for late-onset dementia (24-26,28-30). This underlines the importance of an intellectual enrichment since young age as well as the intervention of public health programs aimed to counteract social discomfort to provide benefits including a decreased risk of neurodegenerative diseases (29).

The positive association between EOD and other mental disorders is not entirely unexpected. Anxiety, depression and a change of behavior can occur more often in younger than in older persons with dementia. Most studies reported a depression prevalence of 20–30% in EOD patients, but the range is very wide due to difficulties in measuring depression in dementia (71). Even if it was thought that the prevalence of depressive symptoms and syndromic depression in AD depends on the severity of dementia and on the scales used for their detection (72), a more recent published systematic review has found no significant relation between the severity of AD and the prevalence of depression (73). Nevertheless, it seems clear that major depression can afflict up to 30% of AD patients and is more often seen in persons with a history of previous depression and a younger age at onset of dementia. In addition, depression in younger patients with dementia can be difficult to diagnose even if persistent depression is a common pre-dementia diagnosis in many types of EOD. In some instances, what is initially attributed to depression turns out to be apathy and social withdrawal due to frontal-executive impairment as early frontal lobe damage is common in many types of EOD, such as FTD (74), thus we cannot exclude that the positive association found in some of the included studies might be related to initial symptoms of dementia.

Our review supports the inverse association between healthy lifestyles (75) and in particular of healthy dietary habits with EOD (76-80). Possible mechanisms of such positive effect on dementia may be related to high intake of nutrients including lutein, folate, vitamin E, beta carotene, polyphenols or n-3 fatty acids (81,82) which can enhance antioxidant capacity and reduce inflammation (83). In addition, high adherence to Mediterranean and DASH diets have been associated with higher potassium and lower sodium intake (84,85). The consequent lowering effects on blood pressure (86-88) and on risk of cardiovascular diseases (89,90) may also affect risk of dementia as suggested in previous studies (91,92).

Our review suffers from some limitations linked to the characteristics of the included studies. As regards the disease, EOD is a disorder characterized by heterogenous clinical presentations (4) and also delay in diagnosis (93), thus studies relied on medical records for case identification may have been affected by selection bias. In addition, most included studies lumped together all the EOD forms, thus preventing the investigation of specific causal relations with the single EOD subtypes. As regards exposure assessment, studies using self-report questionnaires may present exposure misclassification and recall bias, especially case-control studies. Many studies failed to adequately assess the timing of exposure, thus limiting the reliability of such assessment and of its causal relation with the outcome, and also increasing heterogeneity. Moreover, different strategies for the control of confounders were used in the reviewed studies, and this could affect both the validity and the strength of the associations observed, limiting their comparability across studies. Finally, another major issue is the lack of information or the inadequate adjustment for genetic factors such as *ApoE* gene alleles as found in most of the included studies.

Conclusions

The literature on environmental risk factors for EOD has been considerably growing in the most recent years. Overall, it appears to support an association between environmental factors and disease risk. However, additional high-quality research is required to confirm these relations and assess their causal nature.

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