

Online Resource 4: Tables including the data extraction results

*Social Psychiatry and Psychiatric Epidemiology*

**Do prenatal factors shape the risk for dementia?: A systematic review of the epidemiological evidence for the prenatal origins of dementia**

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Table A – Basic information

Parental age and birth order

| Author                              | Ref. | Publication year | N <sup>a</sup>                       | Men/women                                     | Location                                     | Population                                                                                                       | Exposure                                                                         | Exposure ascertainment                                                                                                                                           | Comparison/control                                                                                    |
|-------------------------------------|------|------------------|--------------------------------------|-----------------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Parental age and birth order</b> |      |                  |                                      |                                               |                                              |                                                                                                                  |                                                                                  |                                                                                                                                                                  |                                                                                                       |
| <i>Case-control studies</i>         |      |                  |                                      |                                               |                                              |                                                                                                                  |                                                                                  |                                                                                                                                                                  |                                                                                                       |
| Amaducci                            | 60   | 1986             | 329                                  | 82/150 (excluding population controls)        | Italy; seven centers throughout the country  | Patients from neurology departments, hospital and population control groups                                      | Maternal age (>40)<br>Paternal age (>44)<br>Birth order (≥2)<br>Birth order (≥4) | Next-of-kin interview (for cases and controls)                                                                                                                   | Community controls and hospital controls <sup>a</sup>                                                 |
| Bertram                             | 45   | 1998             | 154                                  | Unclear                                       | Germany                                      | Patients from outpatient clinic, Caucasian                                                                       | Maternal age<br>Paternal age                                                     | Family history questionnaire completed by proxy; not clear if a proxy was also used for the controls                                                             | Age and sex matched volunteers; no family history of dementia; scored ≥ 28 on MMSE                    |
| Chandra                             | 63   | 1987             | 128                                  | 30/98                                         | Denver, Colorado, USA                        | Participants from outpatient clinic for senior citizen's                                                         | Birth order (≥4)                                                                 | Surrogate/next of kin respondent (for cases and controls)                                                                                                        | Patients without dementia from the same outpatient clinic, affected by one or more medical conditions |
| Clarnette                           | 46   | 1992             | Maternal age: 332; paternal age: 318 | For cases (including 56 none AD cases) 98/116 | Hamilton, Canada                             | Referrals to a memory clinic and their spouses                                                                   | Maternal age<br>Paternal age                                                     | From subjects and/or relatives; often verified from family documents                                                                                             | Spouses                                                                                               |
| Cohen                               | 43   | 1982             | 670 (80 cases)                       | For cases 50/30                               | Washington state, USA                        | Patients from community AD registry, Caucasians born between 1891 and 1921; controls from selected birth records | Maternal age                                                                     | Cases: Questionnaire sent to family members; when possible (half of the cases) also through family records and birth certificates<br>Controls: via birth records | Randomly selected birth records for persons born in 1907 in Washington state in 1907                  |
| Corkin                              | 42   | 1983             | 71                                   | 34/37                                         | Massachusetts, USA                           | Participants from research studies on aging and dementia                                                         | Maternal age<br>Paternal age                                                     | Interview with participants. If necessary obtained from or verified by relatives.                                                                                | Spouses without dementia (12/34) and volunteers (12/34) of similar age and SES                        |
| De Braekeleer                       | 44   | 1988             | 133 cases                            |                                               | Saguenay-Lac-St-Jean (SLSJ) region, isolated | Inhabitants of the SLSJ region                                                                                   | Maternal age<br>Paternal age<br>Birth order                                      | Population registry                                                                                                                                              | Comparison with siblings, spouses and six control groups (parental age); Siblings (birth order)       |

|             |    |      |                                                     |              |                                     |                                                                                                                                                                                                                     |                                             |                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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|             |    |      |                                                     |              | region,<br>Canada                   |                                                                                                                                                                                                                     |                                             |                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| English     | 47 | 1985 | 163                                                 | Not reported | Washington state, USA               | Cases: from a hospital and from a self-help organization for relatives of persons with AD<br>Controls: spouses from AD and Parkinson patients.                                                                      | Maternal age                                | Questionnaire filled in by participant (controls) or by relative (cases)                                                                                        | Spouses of the AD patients and spouses form Parkinson patients                                                                                                                                                                                                                                                                                                                                                                                   |
| Farrer      | 33 | 1991 | 1422                                                | 570/852      | Massachusetts , USA                 | Cases: from hospital<br>Controls: from Framingham study                                                                                                                                                             | Maternal age<br>Paternal age                | Cases: informant interview<br>Controls: collected from Framingham study records                                                                                 | Participants of the Framingham study                                                                                                                                                                                                                                                                                                                                                                                                             |
| Farrer      | 59 | 1997 | 2091                                                | 928/1163     | USA                                 | Cases: form different hospitals in the MIRAGE project<br>Controls: from Framingham study                                                                                                                            | Maternal age<br>Paternal age                | Cases: from family history questionnaire by informant; verified by other informants and available medical records<br>Controls: from parental death certificates | Participants of the Framingham study                                                                                                                                                                                                                                                                                                                                                                                                             |
| Forster     | 48 | 1995 | 218                                                 | 96/122       | Northern health region of England   | Cases: patients referred to specialist hospital services, who had been diagnosed as having dementia before the age of 65 years during the period 1981-89<br>Controls: randomly selected from the general population | Maternal age                                | All data concerning history of exposure in both cases and controls were obtained from informants                                                                | Controls were randomly selected from the population of the northern health region by a two stage procedure. Firstly, for each case, a family health service authority (FHSA) was chosen randomly. The authority then supplied the names of five individuals of the same sex and age as the case. If needed a replacement control from the potential list of five was selected randomly. The possibility of dementia in the control was excluded. |
| Fratiglioni | 61 | 1993 | 364                                                 | 67/297       | Stockholm, Sweden                   | Inhabitants from an area in Stockholm that participated in the Kungsholmen project and underwent the MMSE                                                                                                           | Maternal age<br>Paternal age<br>Birth order | Structured interview with informant (close relative or other significant person)                                                                                | Subjects who had MMSE $\geq 34$ and were not diagnosed as affected by dementia in the Kungsholmen project                                                                                                                                                                                                                                                                                                                                        |
| Graves      | 49 | 1990 | 260; 188 and 162 in maternal /paternal age analyses | 140/120      | Seattle area, Washington state, USA | Patients from two clinics; cases and controls were all married for $\geq 10$ years                                                                                                                                  | Maternal age<br>Paternal age                | Structured telephone interview with surrogate                                                                                                                   | Friend of the patient or a patient surrogate; else a relative not related by blood                                                                                                                                                                                                                                                                                                                                                               |

|                |    |      |     |              |                                                                                                  |                                                                                                                                                                                                                                            |                                                      |                                                                                                                                                                                                    |                                                                                                                                                         |
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| Heyman         | 41 | 1983 | 72  | Not reported | 1/2 North Carolina, 1/3 other southeastern states, else from northeastern/midwestern states, USA | Consecutive series of AD patients that had participated in a comprehensive clinical, genetic and epidemiological study of AD at Duke University Medical Center and their spouses                                                           | Maternal age<br>Paternal age                         | Determined with interview. For cases interview with informant (usually the spouse)                                                                                                                 | Close relative, usually the spouse                                                                                                                      |
| Hofman         | 50 | 1990 | 368 | Not reported | Four northern provinces and Rotterdam area, Netherlands                                          | Part of a case-control study of AD, Diagnosis <70                                                                                                                                                                                          | Maternal age<br>Paternal age<br>Birth order          | Structured interview with next of kin (mostly from wife, husband or a child); Information was checked by either the municipal population register or information from a second family member       | Randomly selected from the municipal population register; SPMSQ score $\geq 20$ and apparently healthy                                                  |
| Jouan-flahault | 54 | 1989 | 180 | Not reported | Haute-Normandie, France                                                                          | Elderly population in Haute-Normandie, living at home or in an institution (random sample)                                                                                                                                                 | Maternal age<br>Paternal age                         | Birth records and registry data from birth municipality                                                                                                                                            | Two matched controls per case; from the same population as cases but without an indication for dementia                                                 |
| Knesevich      | 51 | 1982 | 94  | Not reported | Washington, USA                                                                                  | From memory and aging project at the Washington University Medical Center; Caucasian                                                                                                                                                       | Maternal age                                         | Obtained from vital statistics records (official government records), or else records from funeral parlors, monument companies, cemeteries and crematories, cross-checked against family documents | Healthy individuals who had good intellectual function in relation to past performance                                                                  |
|                |    |      |     |              |                                                                                                  |                                                                                                                                                                                                                                            | Birth order                                          | No description                                                                                                                                                                                     | Comparison with the general US population form vital statistic rates in the US 1900-1940                                                                |
| Li             | 64 | 1992 | 210 | 99/111       | Beijing, people's republic of China                                                              | Cases: outpatients and inpatients mostly from two psychiatric hospitals and neurologic clinics in two general hospitals                                                                                                                    | Birth order ( $\geq 4$ )<br>Birth order ( $\geq 6$ ) | Structured and standardized interview with surrogate informants                                                                                                                                    | Controls from neighborhoods of the patients. MMSE > 20                                                                                                  |
| Lindsay        | 40 | 1994 | 793 | Not reported | Canada (all provinces)                                                                           | Cases and controls from community and institutions, drawn from lists of community residents in 36 cities and surrounding areas based on health insurance plans (universal coverage); In Ontario, the Enumeration Composite Record was used | Maternal age<br>Paternal age                         | Interview by informant for cases and controls                                                                                                                                                      | Selected from community and institution (like cases), with normal cognitive functioning according to test                                               |
| Moceri         | 52 | 2000 | 770 | 282/488      | Seattle, Washington, USA                                                                         | Cases: from the University of Washington/GHC AD Patient registry (ADPR).                                                                                                                                                                   | Maternal age<br>Birth order                          | Structured interview by research nurses with informants                                                                                                                                            | Selected at random from the health maintenance organization; did not have dementia or other neurologic disease causing dementia; MMSE score $\geq 28$ . |

|         |    |      |       |                                                   |                                                                                     |                                                                                                                                                                                                       |                                             |                                                                                                                                       |                                                                                                                                                          |
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|         |    |      |       |                                                   |                                                                                     | Controls: from a health-maintenance organization. Representative for population in area, although slightly higher educated                                                                            |                                             |                                                                                                                                       |                                                                                                                                                          |
| Moceri  | 35 | 2001 | 484   | 184/300                                           | Seattle, Washington, USA                                                            | Cases: from the University of Washington/GHC AD Patient registry (ADPR)<br>Controls: from a health-maintenance organization; representative for population in area, although slightly higher educated | Maternal age<br>Paternal age<br>Birth order | From birth certificate or calculated from ages listed on the U.S. census; if they differed birth certificate was used                 | Selected at random from the health maintenance organization; did not have dementia or other neurologic disease causing dementia                          |
| Prince  | 36 | 1994 | 273   | Not reported                                      | England, Scotland and Wales                                                         | Participants form primary care practices participating in the MRC hypertension trial                                                                                                                  | Maternal age (>34)<br>Paternal age (>37)    | Risk factor questionnaires by MRC research nurses to the subject and an informant for each participant                                | Unimpaired, unmatched control from same population with intact PALT scores                                                                               |
| Ptok    | 37 | 2000 | 238   | 85/153                                            | Bonn, Germany                                                                       | Consecutive patients recruited form hospital admissions, controls randomly chosen from general population                                                                                             | Maternal age<br>Paternal age                | Interview with patients, controls and their relatives; only used if there was consistency among relatives and no doubt about accuracy | Healthy control subjects from the general population, chosen with city census agencies                                                                   |
| Tsolaki | 38 | 1997 | 134   | 62/72                                             | Pilea, Thessaloniki, Greece                                                         | Greek residents examined under WHO Program of Aging in 1992; cases were outpatients from Neurology department in Thessaloniki                                                                         | Maternal age<br>Paternal age                | Interview by trained nurses with informant (a close relative, a distant relative, a friend, neighbor or another significant person    | Community controls, MMSE>24, no dementia; similar in age and gender with the cases                                                                       |
| Urakami | 53 | 1989 | 220   | 92/128                                            | Daisen and Kishimoto, Tottori Prefecture and Ama, Shimane Prefecture, Western Japan | Community-based study; participants involved in agriculture, industry and commerce; all fathers were wedded husbands                                                                                  | Maternal age<br>Paternal age                | Birth records                                                                                                                         | Controls subject from persons with about the same age and with a similar socioeconomic status who did not have dementia and who were from the same areas |
| Whalley | 62 | 1982 | 276   | Cases 20/54 (5 excluded in parental age analysis) | Edinburgh, Scotland                                                                 | Subjects from records in the Neuropathology Department, admission to mental hospital before age 65                                                                                                    | Maternal age<br>Paternal age<br>Birth order | From Scottish public registry, calculated from marriage certificates                                                                  | Entries in the same local register*                                                                                                                      |
| Whalley | 34 | 1995 | 2230* | 1035/1185*                                        | Scotland                                                                            | Records of Scottish Mental Hospitals                                                                                                                                                                  | Maternal age<br>Paternal age                | From marriage certificates or else from their birth or death certificates                                                             | Control selection was not reported                                                                                                                       |

|                |    |      |       |                         |                            |                                                                                                                                                                                                                         |                                                                           |                                                                                                                                                                          |                                                                                                                                           |
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| White          | 39 | 1986 | 405   |                         | Minnesota, USA             | Cases died in six of the seven Minnesota state hospitals and the only state nursing home; siblings and controls selected from the same time period as the cases                                                         | Maternal age<br>Paternal age<br>Birth order                               | Cases: interview of a relative (usually more than 1), if possible information was checked by medical birth and death records; not reported for the siblings and controls | Normal siblings of the AD cases and individuals born during the same time period as the cases selected from birth records in Anoka County |
| Cohort studies |    |      |       |                         |                            |                                                                                                                                                                                                                         |                                                                           |                                                                                                                                                                          |                                                                                                                                           |
| Katzman        | 55 | 1989 | 434   | 154/280                 | Bronx, New York, USA       | Subjects were volunteers recruited from senior citizen centers, by local newspaper advertisements, and by word of mouth, aged 75-85 at intake; the majority (70%) were Jewish; the cohort was predominantly (90%) white | Maternal age                                                              | Not specified; probably during interview at first assessment.                                                                                                            | -                                                                                                                                         |
| Kim            | 66 | 2007 | 916   | 376/540                 | Kwangju, South Korea       | Inhabitants age 65 or over, recorded in national residents registration lists within two defined geographic areas (one urban one rural); low-income population.                                                         | Birth order                                                               | Home-based interviews carried out by research nurses, information was collected from participants and family members                                                     | -                                                                                                                                         |
| Lahti          | 67 | 2014 | 13243 | 6905/6338               | Helsinki, Finland          | Helsinki Birth Cohort Study, singleton live births at the two public maternity hospitals in Helsinki, between 1934 and 1944                                                                                             | Maternal grand multiparity (born as sixth or later born child)            | Hospital birth records, grand multiparity defined as being born as sixth or later born child                                                                             | Born as fifth child or earlier                                                                                                            |
| Mosing         | 65 | 2018 | 35191 | 16324-16813/17842-18378 | Sweden                     | All twins, from the Swedish Twin Registry, with information on birth characteristic, born between 1926-1960; excluding early onset dementia cases (<55 years)                                                           | Birth order (within twins)                                                | Based on nationwide collection of information from original birth records, recorded by midwives and/or doctors at the time of birth                                      | -                                                                                                                                         |
| Reisz          | 58 | 2021 | 289   | 0/289                   | Kansas City, Missouri, USA | Caucasian female patients from a community-based out-patient setting in a metropolitan area of the Midwest.                                                                                                             | Maternal age<br>Birth order<br>Age difference with the next older sibling | Exposure variables were collected in a survey                                                                                                                            | -                                                                                                                                         |
| Tyas           | 56 | 2001 | 694   | 261/433                 | Manitoba, Canada           | Random sampling from the provincial insurance plan, all cognitively healthy at start of the study                                                                                                                       | Maternal age<br>Paternal age                                              | Risk factor questionnaire (1991/92)                                                                                                                                      | -                                                                                                                                         |
| Vaillant       | 57 | 2014 | 196   | 196/0                   | Harvard University, USA    | Caucasian sophomore males at Harvard university (born circa 1920), 2/3 of men obtained graduate degrees and most have worked as physicians, lawyers, university professors or business executives                       | Maternal age                                                              | Not clearly reported. Likely from interview (with parents)                                                                                                               | -                                                                                                                                         |

Basic information extracted from studies regarding parental age and/or birth order.

<sup>a</sup>This number represents the participants included in the analyses relevant for our systematic review or, if this specific number was not available, the total number of participants in the study. If the study did not include a control group but used a reference population as a comparison, or if the number of controls was not available, only the number of cases was reported.

\*Reporting was not complete or not clear.

AD=Alzheimer's disease

MMSE=Mini-Mental State Examination

## Season of birth

| Author                      | Ref. | Publication year | N <sup>a</sup> | Men/women    | Location                           | Population                                                                                                  | Exposure                               | Exposure ascertainment                                                                         | Comparison/control                                                                                                                                                                                                                                                              |
|-----------------------------|------|------------------|----------------|--------------|------------------------------------|-------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Season of birth</b>      |      |                  |                |              |                                    |                                                                                                             |                                        |                                                                                                |                                                                                                                                                                                                                                                                                 |
| <i>Case-control studies</i> |      |                  |                |              |                                    |                                                                                                             |                                        |                                                                                                |                                                                                                                                                                                                                                                                                 |
| Dysken                      | 68   | 1991             | 727 cases      | Not reported | St Paul, Cleveland, Chicago, USA   | Cases: from three research departments in a medical center and two universities, born between 1881 and 1940 | Season of birth                        | Based on birth dates (likely from medical records)                                             | Average expected quarterly birth rates for the general US population (1915-1940)                                                                                                                                                                                                |
| Fratiglioni                 | 61   | 1993             | 364            | 67/297       | Stockholm, Sweden                  | Inhabitants from an area in Stockholm that participated in the Kungsholmen project and underwent the MMSE   | Season of birth                        | Swedish registry data                                                                          | Subjects who had MMSE $\geq 34$ and were not diagnosed as affected by dementia in the Kungsholmen project                                                                                                                                                                       |
| Frazee                      | 74   | 2004             | 1359 cases     | Not reported | California, USA                    | Cases: from AD database, birthdates from 1906-1923. Controls from population registry                       | Season and month of birth              | From national registry                                                                         | The monthly distribution of general population birth sin California from 1906-1923                                                                                                                                                                                              |
| Henderson                   | 69   | 1991             | 340            | Not reported | Sydney, Australia                  | Cases: from two Sydney hospitals                                                                            | Season of birth                        | Not clearly reported; based on birthdate                                                       | Controls were recruited from the same or a neighboring general practice as each case and had a MMSE $\geq 26$ ; Also comparison with large population group (n=37534), from the Australian Electoral Roll, for the city of Canberra and its surrounding district of Eden-Monaro |
| Koch                        | 75   | 2005             | 2917           | 692/2225     | Regensburg, Germany                | Patients treated in the psychogeriatric ward of the University clinic of Regensburg between 1995 and 2004   | Season of birth                        | Not reported; likely based on birthdate from patient records                                   | The data was normalized utilizing the overall births per month in Germany (Federal Statistical Office, Wiesbaden, Germany)                                                                                                                                                      |
| Lawlor                      | 72   | 1993             | 306            | Not reported | Not reported; Authors from Ireland | Not reported                                                                                                | Season of birth (first quarter births) | Nor reported; based on birthdate                                                               | 91 age-matched healthy control subjects with no family history of dementia; the number of births per month from an age-matched, census-derived population was also available for comparison                                                                                     |
| Philpot                     | 73   | 1989             | 239 cases      | Not reported | South-East of England              | Cases were consecutive referrals to two hospitals or patients enrolled in the natural history of AD         | Season of birth                        | Not reported; for cases likely from medical records, controls were from the 1971 census sample | Controls were form the 1971 census sample                                                                                                                                                                                                                                       |



|                       |    |      |           |                                    |                                                |                                                                                                                                                          |                           |                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------|----|------|-----------|------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Prince                | 36 | 1994 | 273       | Not reported                       | England, Scotland and Wales                    | Participants form primary care practices participating in the MRC hypertension trial.                                                                    | Season of birth           | Risk factor questionnaires by MRC research nurses to the subject and an informant for each participant | Unimpaired, unmatched controls from the same population with intact PALT scores                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Ptok                  | 70 | 2001 | 238       | 85/153                             | Bonn, Germany                                  | Cases were recruited consecutively from hospital admissions, at least 60 years of age                                                                    | Season of birth           | Not clearly reported; based on birthdate*                                                              | Chosen from the general population with the support of the city census                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Tolppanen             | 76 | 2016 | 353581    | For cases: 24602/46117             | Finland                                        | The Medication and Alzheimer's Disease cohort: community-dwelling persons who received a clinically verified diagnosis of AD in 2005 to 2011             | Month and season of birth | Based on registry data                                                                                 | One to four matched with controls, who were identified from the register including all residents of Finland who are entitled to benefits by the Social Insurance Institution (i.e. all citizens and residents living in Finland for at least two years)                                                                                                                                                                                                                                                                          |
| Vezina                | 80 | 1996 | 399 cases | For cases: 124/275                 | Saguenay–Lac-Saint-Jean (SLSJ), Quebec, Canada | From the Image project in the SLSJ region; all cases were compared to control group 1 and cases born in the SLSJ region were compared to control group 2 | Month of birth            | Not clearly reported; based on birthdate, for controls from databases                                  | Two control groups:<br>1) data obtained from the ministry of health and social services of Quebec. Born between 1893 and 1934 and living in the SLSJ area as of November 1992 or living in that area at the time of their death (1987-1992). Régie de l'assurance-maladie du Quebec, (RAMQ); N=51170).<br><br>2) All births which took place between 1893 and 1934 in SLSJ, computerized register of all the catholic parish record of baptism, marriages and sepultures that took place in the SLSJ (SOREP database; N=135142). |
| Vitiello              | 71 | 1991 | 282       | 130/152                            | Rockville Pike, Bethesda, USA                  | Cases: patients form the unit of Geriatric Psychopharmacology diagnosed with Alzheimer's disease, referred by secondary care providers                   | Season of birth           | Not clearly reported; based on birthdate                                                               | Recruited through the National Institutes of Health volunteer office and advertisements in local newspapers; no evidence of dementia in functioning in the community and performance on neuropsychological screening tests and no history of major psychiatric disorders                                                                                                                                                                                                                                                         |
| <i>Cohort studies</i> |    |      |           |                                    |                                                |                                                                                                                                                          |                           |                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Ding                  | 78 | 2019 | 354859    | 172012/182847<br><br>Cases 496/787 | China                                          | Chinese population, non-institutionalized, representative of total Chinese population                                                                    | Season of birth           | Second China National Sample Survey on Disability in 2006                                              | -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|            |    |      |          |              |                            |                                                                                                                                                                                                            |                                        |                                        |                                             |
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| Doblhammer | 77 | 2015 | 149225   | Not reported | Germany                    | 2% of all insured persons from the largest insurer in Germany (1/3 of German population). Drawn in the first quarter of 2007; SES lower than general population, bias greater in younger than older people | Season and month of birth              | By date of birth in insurer's register | Summer born individuals were the reference  |
| Hsu        | 81 | 2021 | 29074024 | Not reported | Taiwan                     | Taiwanese national health insurance database, covering 99% of Taiwan's population. Born between 1 January 1900 and 31 December 2013                                                                        | Month of birth                         | By date of birth in insurer's register | -                                           |
| Mooldijk   | 79 | 2021 | 12964    | 5478/7486    | Rotterdam, the Netherlands | Participants from the Rotterdam study aged 45 and over. Participants did not have dementia at baseline                                                                                                     | Season of birth and severity of winter | Based on date of birth                 | Summer born individuals were the reference. |

Basic information extracted from studies regarding season of birth.

<sup>a</sup>This number represents the participants included in the analyses relevant for our systematic review or, if this specific number was not available, the total number of participants in the study. If the study did not include a control group but used a reference population as a comparison, or if the number of controls was not available, only the number of cases was reported.

\*Reporting was not complete or not clear.

AD=Alzheimer's disease

MMSE=Mini-Mental State Examination

## Place of birth

| Author                      | Ref. | Publication year | N <sup>a</sup>      | Men/women                                                  | Location                                       | Population                                                                                                                                                                                                          | Exposure                                                   | Exposure ascertainment                                                                                                                                                                 | Comparison/control                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------|------|------------------|---------------------|------------------------------------------------------------|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Place of birth</b>       |      |                  |                     |                                                            |                                                |                                                                                                                                                                                                                     |                                                            |                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                               |
| <i>Case-control studies</i> |      |                  |                     |                                                            |                                                |                                                                                                                                                                                                                     |                                                            |                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                               |
| Baker                       | 83   | 1993             | 72                  | 22/50                                                      | New York city, USA                             | Cases and controls from Burke rehabilitation center; all individuals with cognitive impairment in the past 20 years were evaluated for AD; middle-class community                                                   | Place of birth (rural vs urban?)*                          | Surrogate interview with relative (for cases and controls)                                                                                                                             | In some controls cognitive testing was done (not all), controls were excluded if they had dementia; controls primarily had respiratory and cardiovascular disease.                                                                                                                                                                                                                                            |
| Emard                       | 90   | 1994             | 129 cases only      | Not reported                                               | Saguenay-Lac-Saint-Jean (SLSJ), Quebec, Canada | IMAGE project                                                                                                                                                                                                       | Place of birth (soil composition)                          | A questionnaire was sent to families of cases                                                                                                                                          | No control group; comparison of birth residence soil composition to average municipality composition                                                                                                                                                                                                                                                                                                          |
| Forster                     | 48   | 1995             | 160                 | Not reported                                               | Northern health region of England              | Cases: patients referred to specialist hospital services, who had been diagnosed as having dementia before the age of 65 years during the period 1981-89<br>Controls: randomly selected from the general population | Place of birth (Aluminium concentration in drinking water) | All data concerning history of exposure in both cases and controls were obtained from informants; place of birth was connected to historical data on aluminum levels in drinking water | Controls were randomly selected from the population of the northern health region; for each case, a family health service authority (FHSA) was chosen randomly, the authority then supplied the names of five individuals of the same sex and age as the case; if needed a replacement control from the potential list of five was selected randomly; the possibility of dementia in the control was excluded |
| Frecker                     | 89   | 1991             | 7238 (399 dementia) | 70.4% women in north shore, 53.8% women in rest of the bay | Bonavista bay, Newfoundland, Canada            | Born in the early 1900's; death certificates registered in 1985 and 1986 at the provincial Department of Health                                                                                                     | Place of birth (Drinking water quality)                    | Place of birth from death certificate; aluminum in drinking water and other measures of drinking water quality were performed                                                          | 1985 and 1986 death of individuals born in Bonavista bay surviving beyond age 70 years, and not having a dementing illness recorded on their death certificates                                                                                                                                                                                                                                               |
| Jean                        | 82   | 1996             | 235 cases           | 65/170 for cases                                           | Saguenay-Lac-Saint-Jean (SLSJ), Quebec, Canada | Cases from project IMAGE, comparison with whole SLSJ reference population                                                                                                                                           | Place of birth (rural vs urban)                            | For cases, close family members acted as informants for place of birth; registry data for the reference population<br><br>SLSJ region was divided into urban and rural sub-regions     | Data from the reference population was obtained through the Institut interuniversitaire de recherches sur les populations (IREP), all live births that occurred in the SLSJ within the study period                                                                                                                                                                                                           |

|                       |    |      |         |                                            |                             |                                                                                                                                                                                                                           |                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                            |
|-----------------------|----|------|---------|--------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Prince                | 36 | 1994 | 273     | Not reported                               | England, Scotland and Wales | Participants form primary care practices participating in the MRC hypertension trial                                                                                                                                      | Place of birth (area of residence from birth to age 15; rural vs urban) | Risk factor questionnaires by MRC research nurses to the subject and an informant for each participant                                                                                                                                                                                                                                                                                                                | Unimpaired, unmatched control from same population with intact PALT scores |
| <i>Cohort studies</i> |    |      |         |                                            |                             |                                                                                                                                                                                                                           |                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                            |
| Gilsanz               | 85 | 2017 | 7423    | 3374/4049                                  | San Francisco bay area, USA | Member population of health care delivery system (KPNC), that participated in optional check-ups between 1964 and 1973                                                                                                    | Place of birth (in high stroke mortality state)                         | Place of birth was captured during an optional check-up, asking 'where were you born?'<br><br>High stroke mortality states were determined by using the overall Centers for Disease Control and Prevention stroke mortality rates from 2012 to 2014; high stroke mortality states were those in the top quintiles of stroke mortality rates among US territories (>83 stroke deaths per 100 000 people older than 34) | KPNC members born outside high stroke mortality state                      |
| Gilsanz               | 88 | 2019 | 6268    | 2869/3399                                  | San Francisco bay area, USA | Member population of health care delivery system (KPNC), that participated in optional check-ups between 1964 and 1973                                                                                                    | Place of birth (in high infant mortality rate areas)                    | Place of birth was captured during an optional check-up, asking 'where were you born?'<br><br>State level infant mortality rates were obtained from a historical report issued by the US census bureau from 1928; infant mortality rates were determined separately for white and African-American individuals                                                                                                        | KPNC members born outside high infant mortality rate areas                 |
| Glymour               | 86 | 2011 | 1393733 | Not reported (Comparable to US population) | USA                         | The 2000 US Census Public, individuals who were born in the District of Columbia or any of 49 US states (Excluding Hawaii), self-reporting race as African-American or white; upweighted to represent total US population | Place of birth (Stroke belt)                                            | Place of birth in a 'stroke belt' state, based on the householder who filled in birthplace at the 2000 US census report.                                                                                                                                                                                                                                                                                              | Individuals born outside the stroke belt                                   |
| Guaita                | 92 | 2015 | 1321    | 607/714                                    | Abbiategrosso, Italy        | InveCe.Ab study, residents from Abbiategrosso born between 1935 and 1939                                                                                                                                                  | Place of birth (location in Italy)                                      | Collected from municipal registry and/or from a social questionnaire administered by trained interviewers*                                                                                                                                                                                                                                                                                                            | -                                                                          |
| Scazufca              | 84 | 2008 | 2005    | 784/1221                                   | Butantã, Sao Paulo, Brazil  | Sao Paulo Ageing & Health Study (SPAH); participants lived in 66 pre-defined census sectors of the borough of Butantã with the lowest Human Development Index in the borough.                                             | Place of birth (city, town or rural)                                    | Through interview with participant and a key informant (co-residents, a relative or friend who were familiar with the participants life history); participants were asked to name the place they were                                                                                                                                                                                                                 | -                                                                          |

|         |    |      |        |                |              |                                                                                                                      |                                   |                                                                                                                                                                                                                                                                                                            |                                          |
|---------|----|------|--------|----------------|--------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
|         |    |      |        |                |              | Participants were community-dwelling and recruited through door knocking                                             |                                   | born (farm, town/village, city, district, state, country) and to classify that place as a city (known urban area), town (small village with reduced number of houses, shops and other amenities, and no more than a primary school) or rural area at the time of birth                                     |                                          |
| Topping | 87 | 2021 | 353572 | 220503/133 069 | USA          | Participants from the Diet and Health Study (DHS), including members of the American Association of Retired Persons. | Place of birth (stroke belt)      | State of birth was based on the social security number asked on the initial survey. The stroke belt consists of states with high stroke mortality.                                                                                                                                                         | Individuals born outside the stroke belt |
| Wilson  | 91 | 2005 | 859    | 263/596        | Chicago, USA | Older catholic nuns, priests and brothers from the religious orders study; mean education of 18.1 years.             | Place of birth (county SES level) | Participants (at baseline) were asked the country, state, county and city of their birth; information from the 1920 census (1 in 200) was used to determine the county average Duncan SES index for head of household, literacy rate (in those aged 6 or older), and proportion of 6-13 year old in school | -                                        |

Basic information extracted from studies regarding place of birth.

\*This number represents the participants included in the analyses relevant for our systematic review or, if this specific number was not available, the total number of participants in the study. If the study did not include a control group but used a reference population as a comparison, or if the number of controls was not available, only the number of cases was reported.

\*Reporting was not complete or not clear.

AD=Alzheimer's disease

## Other factors

| Author                      | Ref. | Publication year | N <sup>a</sup>                     | Men/women     | Location                                           | Population                                                                                                                                                                                           | Exposure                                                                                                  | Exposure ascertainment                                                                                                                                                                                                                  | Comparison/control                                                                                                                                                                                                                       |
|-----------------------------|------|------------------|------------------------------------|---------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Other factors</b>        |      |                  |                                    |               |                                                    |                                                                                                                                                                                                      |                                                                                                           |                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                          |
| <i>Case-control studies</i> |      |                  |                                    |               |                                                    |                                                                                                                                                                                                      |                                                                                                           |                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                          |
| Jiang                       | 97   | 2020             | 139                                | 66/73         | Not reported; most likely California, USA          | Recruited from community adult care centers and assisted living facilities.                                                                                                                          | Right hand second to fourth finger length ratio as an indication of prenatal sex hormone exposure (2D:4D) | Images of hands were collected using a scanner. 2D:4D ratios were measured on collected images using a Vernier caliper by a single assessor who was blinded to the group designation of the participants.                               | Controls were from the same population self-reported to have no severe memory impairment or dementia.                                                                                                                                    |
| Vladeanu                    | 96   | 2014             | 40                                 | 18/22         | London, UK                                         | As part of a larger investigation at the Hillingdon Memory Clinic of the Central and North West London National Health Service trust; all were British citizens with English as their first language | The second to fourth finger length ratio as an indication of prenatal sex hormone exposure                | Digital calipers to measure the lengths of the second and fourth fingers, from the crease at the base of the finger to the tip, measured only once; the 2D:4D ratio was calculated for each hand separately and for both hands averaged | Recruited through advertisements in local media; no report of head injury or any diagnosis of a psychiatric disorder or dementia; 16/20 controls received the Addenbrooke Cognitive Examination Revised to test for undiagnosed dementia |
| <i>Cohort studies</i>       |      |                  |                                    |               |                                                    |                                                                                                                                                                                                      |                                                                                                           |                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                          |
| Cocoros                     | 93   | 2018             | 284397                             | 136511/147886 | Denmark                                            | Danish-born residents; registry data                                                                                                                                                                 | Prenatal 1918 influenza pandemic exposure                                                                 | By date of birth, having experienced at least one peak of the 1918 influenza virus in utero, based on Danish surveillance data to identify peaks in the epidemic                                                                        | Unexposed group had birth dates from December 1915 through June 1918 (born before influenza peak) or March through December 1921 (born after the influenza peak and were not in utero during the influenza peak)                         |
| Kang                        | 94   | 2017             | 6790                               | 2778/4012     | Sichuan province, China                            | From rural and urban areas in China                                                                                                                                                                  | Prenatal famine exposure                                                                                  | Based on date of birth; Great Chinese Famine occurred from 1959 to 1961: pre-famine group born between 1956 and 1958, famine group born between 1959 and 1961, post-famine group born between 1962 and 1964                             | Pre-famine group and post-famine group                                                                                                                                                                                                   |
| Lenz                        | 95   | 2018             | Data from 23 nations were included | Not reported  | 23 countries: Australia, Austria, Belgium, Canada, | Analysis done at nation level; participants were mostly white                                                                                                                                        | The second to fourth finger length ratio as an indication of prenatal sex                                 | Online self-measure method for length of the second and fourth fingers; used the mean of the national right-hand and left-hand 2D:4D values; measured in individuals aged 10 to 70 years                                                | Comparison across countries (country averages)                                                                                                                                                                                           |

|     |    |      |       |             |                                                                                                                                                                                                                                                                                      |                                                                     |                                                                                                                                |                                                                                                                                                           |   |
|-----|----|------|-------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---|
|     |    |      |       |             | Croatia,<br>Czech<br>Republic,<br>Denmark,<br>Finland,<br>France,<br>Germany,<br>Hungary,<br>Iceland,<br>Ireland, Italy,<br>Netherlands,<br>New Zealand,<br>Norway,<br>Romania,<br>Spain,<br>Sweden,<br>Switzerland,<br>United<br>Kingdom,<br>and the<br>United States<br>of America |                                                                     | hormone<br>exposure<br>(2D:4D)                                                                                                 |                                                                                                                                                           |   |
| Luo | 98 | 2020 | 43254 | 20632/22622 | Sweden                                                                                                                                                                                                                                                                               | Twins form the Swedish Twin Registry<br>born between 1906 and 1957. | Presumed<br>differential<br>prenatal hormone<br>exposure by<br>comparing same-<br>and opposite- sex<br>dizygotic twin<br>pairs | Based on the Swedish Twin Registry.<br>Comparing those form opposite-sex twin<br>pairs to same-sex dizygotic twin pairs,<br>for men and women separately. | - |

Basic information extracted from studies regarding other factors.

<sup>a</sup>This number represents the participants included in the analyses relevant for our systematic review or, if this specific number was not available, the total number of participants in the study. If the study did not include a control group but used a reference population as a comparison, or if the number of controls was not available, only the number of cases was reported.

\*Reporting was not complete or not clear.

## Birth characteristics

| Author                | Ref. | Publication year | N <sup>a</sup> | Men/women               | Location                    | Population                                                                                                                                                                                              | Exposure                                                                                    | Exposure ascertainment                                                                                                                                                                                                                                                          | Comparison/control                                                             |
|-----------------------|------|------------------|----------------|-------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| <b>Birth size</b>     |      |                  |                |                         |                             |                                                                                                                                                                                                         |                                                                                             |                                                                                                                                                                                                                                                                                 |                                                                                |
| <i>Cohort studies</i> |      |                  |                |                         |                             |                                                                                                                                                                                                         |                                                                                             |                                                                                                                                                                                                                                                                                 |                                                                                |
| Matshushima           | 99   | 2018             | 269            | Not reported            | Hiroshima and Sendai, Japan | From the Japanese Study of Age and Retirement (JSTAR); baseline sample were individuals aged 50 to 75 who were randomly chosen based on household registration in a total of 10 selected municipalities | Low birth weight/premature birth                                                            | Respondents were asked in a questionnaire to fill in their birth weight (in kilograms), if they had it recorded in a birth record handbook or if someone told them and if they did not know the weight, they were requested to answer whether they were a premature baby or not | Individuals not reporting low birth weight or being born preterm               |
| Mosing                | 65   | 2018             | 35191          | 16324-16813/17842-18378 | Sweden                      | All twins, from the Swedish Twin Registry, with information on birth characteristic, born between 1926-1960; excluded early onset dementia (<55 yeas)                                                   | Birth weight<br>Head circumference at birth<br>Birth length<br>Gestational age<br>Birth SES | Based on nationwide collection of information from original birth records, recorded by midwives and/or doctors at the time of birth                                                                                                                                             | Dependent on analysis (e.g individuals not being born small for gestation age) |
| Syddall               | 100  | 2005             | 37615          | 21632/15983             | Hertfordshire, England      | Hertfordshire Cohort study: all births from 1911 were reported by the attending midwife and recorded in ledgers; individuals that could be traced were included                                         | Birth weight                                                                                | Computerized midwife ledgers; birth weight was measured in pounds and ounces and had been converted to metric units, the midwives typically recorded weights to the nearest quarter pound                                                                                       | -                                                                              |

Basic information extracted from studies regarding birth characteristics.

<sup>a</sup>This number represents the participants included in the analyses relevant for our systematic review or, if this specific number was not available, the total number of participants in the study. If the study did not include a control group but used a reference population as a comparison, or if the number of controls was not available, only the number of cases was reported.

\*Reporting was not complete or not clear.

SES=Socioeconomic status



Table B – Information and Results

Parental age and birth order

| Author                       | Ref. | Outcome                              |                                                                                                       |                                                                        | Statistical test                                                         | Covariates accounted for in model or by matching                                    | Exposure                                                                                                                                                     | Results (by exposure)                                                                                                                                                                                           |                      | Key limitations                                                                     |
|------------------------------|------|--------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-------------------------------------------------------------------------------------|
|                              |      | Type                                 | Measurement/criteria                                                                                  | Age; mean (SD; range)                                                  |                                                                          |                                                                                     |                                                                                                                                                              | Unadjusted/crude model                                                                                                                                                                                          | Fully adjusted model |                                                                                     |
| Parental age and birth order |      |                                      |                                                                                                       |                                                                        |                                                                          |                                                                                     |                                                                                                                                                              |                                                                                                                                                                                                                 |                      |                                                                                     |
| Case-control studies         |      |                                      |                                                                                                       |                                                                        |                                                                          |                                                                                     |                                                                                                                                                              |                                                                                                                                                                                                                 |                      |                                                                                     |
| Amaducci                     | 60   | Alzheimer's disease                  | Slow and progressive decline assessed with the Blessed Dementia Scale                                 | (41-80)                                                                | Matched pairs odds ratio and McNemar's test (corrected for continuity)   | Matched on: age ( $\pm 3$ years), sex and region of residence                       | Maternal age $>40$ OR 4.67 (p=0.01)<br>Paternal age $>44$ OR 4.50 (p=0.06)<br>Birth order $\geq 2$ OR 1.28 (p=0.53)<br>Birth order $\geq 4$ OR 1.88 (p=0.06) |                                                                                                                                                                                                                 | -                    | -Extensive multiple testing                                                         |
| Bertram                      | 45   | Alzheimer's disease                  | ICD-10 criteria and NINCDS-ADRDA criteria for probable AD                                             | Cases high MGAD 70.8 (10.9); low MGAD 70.3(9.0)<br>Controls 70.3 (8.9) | Independent student's t-test                                             | Matched on: age and gender                                                          | Maternal age<br>Paternal age                                                                                                                                 | NS<br>NS<br><br>(subgroup results in table C)                                                                                                                                                                   | -                    | -Statistics insufficiently reported                                                 |
| Chandra                      | 63   | Alzheimer's disease (onset after 70) | Short portable mental status questionnaire and medical records; NINCDS-ADRDA criteria for probable AD | Cases 83.2 (70-96); Controls 83.0                                      | Matched pairs odds ratio and McNemar's test                              | Matched on: relationship with surrogate respondent, age (within 3 years), race, sex | Birth order $\geq 4$                                                                                                                                         | OR 1.0, $X^2=0.00$ (NS)                                                                                                                                                                                         | -                    | -Multiple testing<br>-Only late age of onset                                        |
| Clarnette                    | 46   | Alzheimer's disease                  | MMSE and patient history; NINCDS-ADRDA criteria for possible or probable AD                           | Not reported                                                           | Unpaired t-test and odds ratios with 5 year maternal/paternal age groups | -                                                                                   | Maternal age<br><br><br><br><br><br><br><br>Paternal age                                                                                                     | t-test means NS<br>16-20: OR 0.78 (0.31-2.07)<br>21-25: OR 1.33 (0.67-2.62)<br>26-30: reference<br>31-35: OR 1.97 (0.85-4.42)<br>36-40: OR 0.82 (0.35-2.11).<br>41+ OR 2.59 (0.87-10.08)<br><br>t-test means NS | -                    | -No strict protocol for ascertainment of exposure<br>-Not accounting for covariates |

|                    |    |                                                  |                                                                                                    |                                             |                                                                                                               |                                                                                                                                                                                                                                                    |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                           |                               |                                                                                          |
|--------------------|----|--------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------|
|                    |    |                                                  |                                                                                                    |                                             |                                                                                                               |                                                                                                                                                                                                                                                    |                                                         | 16-20: OR 0.95 (0.23-4.27)<br>21-25: OR 1.07 (0.48-2.35)<br>26-30: OR reference<br>31-35: OR 1.08 (0.49-2.35)<br>36-40: OR 3.15 (1.20-7.79)<br>41+ OR 1.48 (0.6-3.6)                                                                                                                                                                                                                                                      |                               |                                                                                          |
|                    |    |                                                  |                                                                                                    |                                             |                                                                                                               |                                                                                                                                                                                                                                                    |                                                         | (subgroup results in table C)                                                                                                                                                                                                                                                                                                                                                                                             |                               |                                                                                          |
| Cohen              | 43 | Alzheimer's disease                              | Classified according the research criteria for AD; extensive list of diagnostic criteria mentioned | Cases 73.2                                  | None, only means reported                                                                                     | -                                                                                                                                                                                                                                                  | Maternal age                                            | Cases mean 35.5 (SE=1.4)<br>Controls mean 27                                                                                                                                                                                                                                                                                                                                                                              | -                             | -Comparison group not clearly described<br>-No statistical analysis                      |
| Corkin             | 42 | Alzheimer's disease                              | Neurologic examination; extensive list of diagnostic criteria mentioned                            | Cases 63.5 (52-78)<br>Controls 63.8 (52-80) | None, only means reported                                                                                     | No matching, they state control data were obtained from individuals of comparable age and SES                                                                                                                                                      | Maternal age<br><br>Paternal age                        | Cases mean 27.7 (18-33)<br>Controls mean 27.4 (17-40)<br><br>Cases mean 30 (21-50)<br>Controls mean 29.4 (18-39)                                                                                                                                                                                                                                                                                                          | -                             | -No statistical analysis                                                                 |
|                    |    |                                                  |                                                                                                    |                                             |                                                                                                               |                                                                                                                                                                                                                                                    |                                                         | (subgroup results in table C)                                                                                                                                                                                                                                                                                                                                                                                             |                               |                                                                                          |
| De Braekeleer 1988 | 44 | Alzheimer's disease (clinical or autopsy proven) | Definite, probable or possible AD according to NINCDS-ADRDA criteria                               | Not reported                                | Two tailed student's paired t-test. Haldane-Smith test (birth order)                                          | Dependent on comparison:<br><br>Siblings and spouses: no matching<br><br>Controls 1-2-3 matched on: date of parental marriage (+/- 5 days), parental SES, parental residence, birth rank<br><br>Controls 4-5-6 matched on: Sex, year of birth, SES | Maternal age<br><br><br>Paternal age<br><br>Birth order | Cases mean 29.4 (SD 6.7)<br>Siblings mean 31.5 (SD 4.1)<br>F=2.64 p<0.001<br>Vs spouses (mean 29.5 (SD 6.1) or controls p>0.10<br><br>Cases mean 32.6 (SD 7.5)<br>Siblings mean 34.9 (SD 5.0)<br>F=2.25 p=0.001<br>Vs spouses (mean 33.4 (SD 6.7) or controls p>0.10<br><br>Test-statistic: -3.075, p>0.99 (no birth order effect vs later born alternative), no birth order effect vs early birth order effect (p<0.001) | -                             | -Limited reporting                                                                       |
| English            | 47 | Alzheimer's disease                              | Thorough physical and psychiatric examination                                                      | Not reported                                | Chi-squared test for trend; Mantel's test for trend to include covariates; 95% CIs for odds ratios calculated | Adjustment for mother's year of birth (10 year interval)                                                                                                                                                                                           | Maternal age                                            | <25 reference<br>25-29: OR 0.4 (0.17-1.1)<br>30-34: OR 1.0 (0.38-2.4)<br>35-39: OR 0.7 (0.21-2.3)<br>40+: OR 1.4 (0.22-9.1)<br>p=0.82                                                                                                                                                                                                                                                                                     | Similar results, not reported | -Low response rate<br>-Method of exposure ascertainment different for cases and controls |

|                               |    |                                                  |                                                                                                                      |                                         | by Cornfields method                                                                                                        | (subgroup results in table C)                                                                                                                                                                                       |              |                                                                                                                 |                                                                                                                |                                                                                                                           |
|-------------------------------|----|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Farrer 1991                   | 33 | Alzheimer's disease                              | Probable AD according to NINCDS-ADRD criteria                                                                        | Not reported; age at onset 67.2 (42-86) | Matched design: paired comparison t-test and conditional logistic regression                                                | Matched on: sex, year of birth (same year), 'survival' age and *residence<br><br>Included in conditional logistic model: parental and maternal age in one model*                                                    | Maternal age | AD mean 27.4 (SE 0.4)<br>Control 27.9 (SE 0.2) NS<br>OR 1.04 (0.89-1.23) (5-year steps)                         | -                                                                                                              | -Limited reporting                                                                                                        |
|                               |    |                                                  |                                                                                                                      |                                         |                                                                                                                             |                                                                                                                                                                                                                     | Paternal age | AD 30.5 (SE 0.5)<br>Control 31.6 (SE 0.2) NS<br>OR 0.88 (0.76-1.01) (5-year steps)                              |                                                                                                                |                                                                                                                           |
| (subgroup results in table C) |    |                                                  |                                                                                                                      |                                         |                                                                                                                             |                                                                                                                                                                                                                     |              |                                                                                                                 |                                                                                                                |                                                                                                                           |
| Farrer 1997                   | 59 | Alzheimer's disease (clinical or autopsy proven) | Definite or probable AD according to NINCDS-ADRD criteria                                                            | Not reported                            | Least square mean/Duncan multiple range test (taking matching into account)<br><br>Conditional logistic regression analysis | Matched on: gender, year of birth (wide intervals), 'survival' age<br><br>Adjusted for:<br>(1) Gender, age/year of birth (least square means)<br><br>(2) APOE genotype, maternal/paternal age (logistic regression) | Maternal age | Cases mean 28.9 control 28.1 p<0.02<br>OR 1.28 (1.08-1.48) (10 year steps)                                      | OR 1.12 (0.88-1.41) (10 year steps)                                                                            | -AD cases form clinic<br>-Concerns of recruitment bias<br>-There might be some overlap with participants from Farrer 1991 |
|                               |    |                                                  |                                                                                                                      |                                         |                                                                                                                             |                                                                                                                                                                                                                     | Paternal age | Cases mean 32.1 controls 31.0 p=0.004<br>OR 1.22 (1.06-1.40) (10 year steps)                                    | OR 1.16 (0.96-1.41) (10 year steps)                                                                            |                                                                                                                           |
| (subgroup results in table C) |    |                                                  |                                                                                                                      |                                         |                                                                                                                             |                                                                                                                                                                                                                     |              |                                                                                                                 |                                                                                                                |                                                                                                                           |
| Forster                       | 48 | Presenile Alzheimer's disease (onset <65)        | Hospital cases notes were studied; DSM-III-R criteria for dementia, NINCDS-ADRD criteria for Alzheimer's disease     | Not reported; diagnoses <65             | OR's calculated with McNemar's test (taking matching into account)                                                          | Matched on: age and sex                                                                                                                                                                                             | Maternal age | Maternal age >=40 0.4<br>95%CI 0.1-1.59 p=NS                                                                    |                                                                                                                | -Multiple testing<br>-Only included early onset AD                                                                        |
| Fratiglioni                   | 61 | Alzheimer's disease                              | MMSE screening, DSM III-R criteria with some modifications; mild, moderate or severe dementia according to CDR scale | >75                                     | ORs, Logistic regression                                                                                                    | Adjustment for: age, sex, education, type of informant<br><br>Birth order: also adjusted for number of siblings                                                                                                     | Maternal age | <25 reference<br>25-34 OR 2.1 (1.0-4.5)<br>35+ OR 2.0 (0.6-4.5)                                                 | <25 reference<br>25-34 OR 2.2 (1.0-4.9)<br>35+ OR 2.0 (0.8-4.7)                                                |                                                                                                                           |
|                               |    |                                                  |                                                                                                                      |                                         |                                                                                                                             |                                                                                                                                                                                                                     | Paternal age | <25 reference<br>25-34 OR 0.9 (0.4-2.1)<br>35+ OR 1.5 (0.7-3.6)                                                 | <25 reference<br>25-34 OR 1.0 (0.4-2.3)<br>35+ OR 1.6 (0.7-3.9)                                                |                                                                                                                           |
|                               |    |                                                  |                                                                                                                      |                                         |                                                                                                                             |                                                                                                                                                                                                                     | Birth order  | 2 <sup>nd</sup> vs 1 <sup>st</sup> OR 1.2 (0.7-2.03)<br>4+ vs 1 <sup>st</sup> -3 <sup>th</sup> OR 1.3 (0.8-2.2) | 2 <sup>nd</sup> vs 1 <sup>st</sup> OR 1.0 (0.6-1.8)<br>4+ vs 1 <sup>st</sup> -3 <sup>th</sup> OR 1.0 (0.5-1.9) |                                                                                                                           |

[illegible]

|             |    |                                                            |                                                                                                                             |                                                                        |                                                    |                                                                                                                                                                                |                                                     |                                                                                                                                                                                                                                                  |   |                                                                                                   |
|-------------|----|------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---------------------------------------------------------------------------------------------------|
|             |    |                                                            | deterioration at home interview                                                                                             |                                                                        |                                                    |                                                                                                                                                                                |                                                     | Mean cases 31.6 controls 33.0 NS                                                                                                                                                                                                                 |   |                                                                                                   |
| Knesevich   | 51 | Alzheimer's disease (clinical diagnosis or autopsy proven) | Diagnostic criteria (Berg et al.); additional subjects with autopsy proven Alzheimer's disease                              | Not reported                                                           | T-test (maternal age), Slater method (birth order) |                                                                                                                                                                                | Maternal age                                        | NS                                                                                                                                                                                                                                               | - | -Limited sample-size<br>-Comparison with population from a different decade<br>-Limited reporting |
|             |    |                                                            |                                                                                                                             |                                                                        |                                                    |                                                                                                                                                                                | Birth order                                         | Cases mean 0.41 (on a 0-1 scale; SE 0.082)<br>Controls mean 0.47 (on a 0-1 scale; SE 0.083) NS                                                                                                                                                   |   |                                                                                                   |
| Li          | 64 | Alzheimer's disease (onset >40)                            | NINCDS-ADRDA criteria for probable AD and ICD-10 criteria for dementia in AD; all followed for 6 months                     | Cases 65.2, Controls 65.4                                              | 1:2 matched set method of analysis, OR             | Matched on: age (3 years) and sex                                                                                                                                              | Birth order ≥4<br>Birth order ≥6                    | OR 1.47 (0.73-2.97)<br>OR 2.75 (0.71-10.67)                                                                                                                                                                                                      | - | -Extensive multiple testing<br>-Young patients                                                    |
| Lindsay     | 40 | Alzheimer's disease                                        | Modified MMSE (3MS), clinical examination if indication by MMSE. DSM-III-R criteria + NINCDS-ADRDA criteria for probable AD | Cases 84.7 Controls 79.0                                               | Unconditional logistic regression                  | Frequency matched on: age group, study center and residence in community of institution.<br><br>Included in model: Age, sex, education, residence in community or institution. | Maternal age<br><br>Paternal age                    | -<br><br><20 OR 1.86 95%CI 0.52-6.61<br>20-29 reference<br><br>>40 OR 1.49 95%CI 0.71-3.16<br>20-29 reference                                                                                                                                    |   | -Limited reporting<br>-Extensive multiple testing                                                 |
| Moceri 2000 | 52 | Alzheimer's disease                                        | DSM-3th revised and definite or probable AD according to NINCDS-ADRDA criteria                                              | Most between 60-9; mean age at intake cases 78 (6.7) controls 78 (6.8) | Unconditional logistic regression                  | Frequency matched on: sex and age (2 years)                                                                                                                                    | Maternal age<br><br>Birth order                     | <20 OR 1.02 (0.53-1.95)<br>20-34 referent<br>35+ 0.89 (0.71-1.12)<br><br>OR 1.04 (0.96-1.12)                                                                                                                                                     | - | -Multiple testing                                                                                 |
| Moceri 2001 | 35 | Alzheimer's disease                                        | DSM-3th revised and probable AD according to NINCDS-ADRDA criteria                                                          | Most between 60-89; not clearly reported                               | Unconditional logistic regression                  | Frequency matched on: sex and age (2 years)                                                                                                                                    | Maternal age<br><br>Paternal age<br><br>Birth order | <20 OR 0.75 (0.28-1.95)<br>20-24 reference<br>35+ OR 0.86 (0.72-1.19)<br><br><20 OR 1.07 (0.00-39.61)<br>20-34 reference<br>35+ OR 1.11 (0.75-1.63)<br><br>1st reference<br>2nd 1.58 (0.95-2.61)<br>3rd 1.12 (0.62-2.02)<br>4th 1.24 (0.74-2.09) | - | -Multiple testing<br>-There might be some overlap with participants included in Moceri 2000       |

|           |    |                                                      |                                                                                                                                                                             |                                                                                                                                  |                                                                                     |                                                                                                      |                                              |                                                                                                                                                                                                                                                                                                                  |                                                   |                                                                           |
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| Prince    | 36 | Alzheimer's disease and other dementias (onset > 65) | DSM-III-R criteria for dementia including AD, multi-infarct dementia, mixed vascular and AD and amnesic syndrome. Possible or probable AD according to NINCDS-ARDA criteria | 71-87                                                                                                                            | Odds ratios; logistic regression for adjusted analysis                              | Included in adjusted model: age, sex, family history of dementia, premorbid IQ and area of residence | Maternal age >34NS<br>Paternal age >37 NS    | NS<br>NS                                                                                                                                                                                                                                                                                                         | -Very limited reporting                           |                                                                           |
| Ptok 2000 | 37 | Alzheimer's disease                                  | Possible AD according to NINCDA-ADRDA criteria; CIDI and SIDAM interviews                                                                                                   | >60<br>AD patients<br>76.99 (9.66)<br>Controls<br>76.99 (9.66)                                                                   | ANOVA                                                                               | Included in adjusted model: gender<br><br>Matched on: age, gender and education                      | Maternal age<br><br>Paternal age             | AD mean 28.13 (SD 5.59 95%CI 26.60-29.66)<br>Depression and AD 29.13 (SD 5.01 27.32-30.93)<br>Controls 28.10 (SD 5.32 26.98-29.23)<br>F=0.548 df=4 p=0.701<br><br>AD 32.67 (SD 8.70 30.14-35.19)<br>Depression and AD 32.80 (SD 6.86 30.24-35.36)<br>Controls 31.79 (SD 5.84 30.54-33.04)<br>F=0.292 df=4 p=0.88 | No relevance of the subject's gender was detected | -Limited reporting<br>-Low availability of parental age data              |
| Tsolaki   | 38 | Alzheimer's disease                                  | DSM-IV and NINCDS-ADRDA criteria for probable AD                                                                                                                            | >70                                                                                                                              | Chi-square (Yates's correction if necessary), logistic regression, cluster analysis | Age-matched?*                                                                                        | Maternal age (>35)<br><br>Paternal age (>35) | Chi-squared p=0.8<br>Cases: 21 women, 7 men<br>Controls: 13 women, 4 men with maternal age >35<br><br>Chi-squared p=0.92<br>Cases: 11 women and 12 men<br>Controls: 8 women and 10 men with paternal age >35                                                                                                     | -                                                 | -Multiple testing<br>-Limited reporting related to case/control selection |
| Urakami   | 53 | Alzheimer's disease, Multi-infarct dementia (MID)    | DSM-III and NINCDS-ADRDA criteria; Hachinski ischemia score to distinguish AD from MID, followed at least 3 years                                                           | AD 80.78 (7.64)<br>MID 78.46 (8.90)<br>Controls normal cognition<br>77.97 (7.52)<br>Controls subnormal cognition<br>78.07 (7.52) | Student's t-test                                                                    |                                                                                                      | Maternal age<br><br>Paternal age             | AD 26.58 (SD 6.63)<br>MID 24.12 (SD 5.73)<br>Normal 23.86 (SD 4.85)<br>Subnormal 25.00 (SD 5.46)<br>AD vs MID p<0.02<br>AD vs normal sign. higher<br><br>AD 31.44 (SD 8.65)<br>MID 27.21 (SD 6.99)<br>Normal 26.29 (SD 5.65)<br>Subnormal 27.91 (SD 6.08)                                                        | -                                                 | -Limited reporting<br>-Limited numbers                                    |

|              |    |                                                             |                                                                                                                                                                         |                                                      |                                                                                                                      |                                                                                                                                                                                |                                                             |                                                                                                                                                                                                                                                                                                                                               |                                                                                         |                                         |
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|              |    |                                                             |                                                                                                                                                                         |                                                      |                                                                                                                      |                                                                                                                                                                                |                                                             | AD vs normal p<0.001<br>AD vs subnormal p<0.01<br>AD vs MID sign. higher                                                                                                                                                                                                                                                                      |                                                                                         |                                         |
| Whalley 1982 | 62 | Alzheimer's disease (autopsy proven)                        | Admission to mental hospital before age 65; clinical characteristics; neuropathological evidence from autopsy                                                           | Age at death, men 62.3 (SD 6.7), women 64.4 (SD 4.7) | Paired students t-test (parental age)<br><br>Tendency to be born later with method of Carothers et al. (birth order) | 1:3 matched for date of entry birth record, sex and social class                                                                                                               | Maternal age<br><br><br>Paternal age<br><br><br>Birth order | Cases mean 30.6 (SE 0.7)<br>Controls mean 28.6 (SE 0.4) p=0.014<br>Sibling control NS<br><br>Cases mean 33.2 (SE 0.8)<br>Controls mean 30.8 (SE 0.5) p=0.005<br>Sibling control NS<br><br>NS                                                                                                                                                  | -                                                                                       | -Limited reporting                      |
| Whalley 1995 | 34 | Alzheimer's disease, vascular dementia (symptoms before 65) | Probable presenile AD according to McKhann criteria; Hachinski score greater than 6 and at least one cerebrovascular accident additional criteria for vascular dementia | <73; symptoms present before 65                      | Conditional logistic regression                                                                                      | Matched on: sex, birth registration district, date of birth (same year), father's occupational group<br><br>Included in adjusted model: parental and maternal age in one model | Maternal age<br><br><br>Paternal age                        | AD mean 30.17 (SD 6.27)<br>controls 28.82 (SD 6.14) NS<br>VaD mean 28.80 (SD 6.03)<br>controls 28.88 (SD 6.02) NS<br><br>AD mean 33.58 (SD 7.44)<br>controls 31.53 (SD 6.84) p<0.001<br>VaD mean 31.53 (SD 6.69)<br>controls 31.89 (6.87) NS                                                                                                  | AD Likelihood ratio 0.303<br>df=1 p=0.58<br>VaD NS<br><br>AD 1.05 (1.02-1.09)<br>VaD NS |                                         |
|              |    |                                                             |                                                                                                                                                                         |                                                      |                                                                                                                      |                                                                                                                                                                                |                                                             | <i>(subgroup results in table C)</i>                                                                                                                                                                                                                                                                                                          |                                                                                         |                                         |
| White        | 39 | Alzheimer's disease (clinical and autopsy proven)           | Identified from autopsy records. Secondary cases identified from relatives and diagnosed using clinical criteria                                                        | Not reported                                         | One tailed t-test, Sibling analysis                                                                                  | No direct adjustment, they performed a sibling analysis to indirectly accounts for SES and education                                                                           | Maternal age<br><br><br>Paternal age<br><br><br>Birth order | AD mean 29.1<br>normal siblings 27.5<br>t(202)=1.50 df=202 p=0.07<br>controls 30.0<br>t(310)=-1.16 p>0.05<br><br>AD mean 34.2<br>normal siblings 32.9<br>t(203)=0.98 p>0.10<br>controls 34.7<br>t(311)=-0.59 p>0.50<br><br>AD mean 3.10<br>expected average throughout sibship t(120)=1.20 p=0.11<br>Controls mean 4.20<br>t(324)=3.50 p<0.01 | -                                                                                       | -Statistic method not clearly described |

Cohort studies

|         |    |                                                 |                                                                                                                                                                                                                        |                                               |                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                |                                                                                              |                                                                                  |                                                                                                                                                                                                                 |
|---------|----|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Katzman | 55 | Alzheimer's disease                             | If a change in cognition or function was noted, or if there was an increase of four errors or more on the IMC or if the total errors exceeded eight, a dementia work-up was carried out. DSM-III and McKhannn criteria | 79 (75-85) at intake                          | Chi-squared test                                                              | -                                                                                                                                                                                                                                                                                                                                                                                                      | Maternal age                                                   | Mean maternal age at birth<br>Alzheimer cases: 25<br>No dementia: 26<br><br>NS               | -                                                                                | -Limited reporting<br>-Results/statistics insufficiently reported for our exposure of interest                                                                                                                  |
|         |    |                                                 | 5-year follow up period                                                                                                                                                                                                |                                               |                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                |                                                                                              |                                                                                  |                                                                                                                                                                                                                 |
| Kim     | 66 | Dementia                                        | Consensus diagnosis of dementia and subtypes were made by three psychiatrists and a neurologist, according to DSM-IV NINCDS-ADRDA and NINDS-AIREN criteria                                                             | Cases 77.9 (6.8)<br>Controls 73.1 (5.2) (>65) | T-test                                                                        | -                                                                                                                                                                                                                                                                                                                                                                                                      | Birth order                                                    | Mean (SD) birth order<br>No dementia: 2.5 (1.6)<br>Dementia: 2.5 (1.7)<br>t=-0.48<br>p=0.631 | -                                                                                | -Not accounting for older age in dementia group<br>-Primary focus was not on birth order as an exposure (limited analysis/reporting)                                                                            |
| Lahti   | 67 | Dementia                                        | Hospital Discharge Register and Causes of Death Register; ICD-8 (290.00-290.10), ICD-9 (290, 2912A, 2928C, 2941A, 3310A, 3311A, 4378A) ICD-10 (F00, F01, F03, F051, G30)                                               | 66-76                                         | Cox proportional hazards models                                               | Model 1: Adjusted for sex, year of birth (1934-1938 or 1939-1944), mother's and father's highest attained occupational statuses, birth weight, maternal body mass index at childbirth<br><br>Model 2: Adjusted for sex, year of birth (1934-1938 or 1939-1944), mother's and father's highest attained occupational statuses, birth weight, maternal BMI at childbirth, and maternal age at childbirth | Maternal grand multiparity (born as sixth or later born child) | Model 1:<br>HR 0.93 95%CI 0.29-2.98, p=0.91<br><br>(subgroup results in table C)             | Model 2:<br>HR 1.09 95%CI 0.34-3.55, p=0.88<br><br>(subgroup results in table C) | -Number of individuals with dementia was really low<br>-No crude model presented<br>-Cohort was born around time of war, malnutrition was common, may limit generalizability to individuals born more recently. |
| Mosing  | 65 | Dementia (clinical diagnosis or cause of death) | Register-based dementia diagnoses as well as date of first diagnosis were derived from the NPR and CDR. ICD 7-10 codes for                                                                                             | 74.3 (2.6; 55-88)                             | Cox proportional hazard analysis; Corrected for correlation within twin pairs | Included in model: sex                                                                                                                                                                                                                                                                                                                                                                                 | Birth order (within twins)                                     | NS (p>0.05)                                                                                  |                                                                                  | -Registry data might miss a lot of dementia diagnosis<br>-Only twins were included                                                                                                                              |



|          |    |                        | AD, vascular dementia<br>and other dementia                                                                                                                                                                                                                                                                                                                   |                                                            |                                                           |                                                                                 |                                                                                 |                                                                                                                                                                                                             |   | (population not<br>representative)                                                                |
|----------|----|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---------------------------------------------------------------------------------------------------|
| Reisz    | 58 | Dementia               | Based on documented<br>diagnosis of dementia in<br>the patient's problem list,<br>current prescription and<br>use of medications used<br>for Alzheimer's dementia,<br>or endorsement of a<br>dementia diagnosis by a<br>caregiver present at the<br>time of the clinic visit                                                                                  | 77.12 (6.8;<br>65-98)                                      | Logistic<br>regression                                    | Age                                                                             | Maternal age<br>Birth order<br>Age difference<br>with the next<br>older sibling | OR 1.026 95%CI 0.963-1.09<br>OR 1.268 95%CI 0.988-1.61<br>OR 1.046 95%CI 0.896-<br>1.205                                                                                                                    |   | -Only Caucasian<br>women were<br>included<br>-Exposure status<br>based on patient<br>recollection |
| Tyas     | 56 | Alzheimer's<br>disease | Individuals with MMSE<br>score <78 were clinically<br>evaluated for AD;<br>NINCDS-ADRDA<br>criteria for probable or<br>possible AD<br><br>5-year follow up period                                                                                                                                                                                             | Cases 79.8<br>(5.7)<br>Controls<br>73.7 (5.7) at<br>intake | Logistic<br>regression                                    | Included in adjusted<br>model: age, sex and<br>education                        | Maternal age<br><br>Paternal age                                                | -<br><br>Cases mean 28.0<br>Controls mean 28.8<br>RR 0.97 95%CI 0.91-1.04<br><br>Cases mean 31.9<br>Controls mean 33.9<br>RR 0.95 95%CI 0.89-1.02                                                           |   | -Limited reporting<br>-Multiple testing<br>-Low number of<br>AD cases                             |
| Vaillant | 57 | Dementia               | Telephone Interview for<br>Cognitive Status (TICS)<br>(at age 80, 85 and 90)<br>score <31 and clinical<br>evidence for dementia<br>(information from<br>relatives, psychosocial<br>course after 70, results<br>from the physical exams<br>conducted every five<br>years, and death<br>certificates)<br><br>Followed from 25-90,<br>survived until at least 70 | At least<br>survived<br>until 70                           | Spearman's rho<br>(two-tailed),<br>logistic<br>regression | Did not adjust for factors,<br>however, this was a very<br>uniform group of men | Maternal age                                                                    | Spearman's rho<br>Dementia by age 90: 0.10<br>(NS)<br>Intact cognition (1) or<br>dementia (0) at age 90<br>(n=84): -0.20 (NS)<br><br>Dementia vs intact cognition<br>at age 90<br><br>OR 0.27 95% 0.06-1.13 | - | -Limited reporting<br>-Sample highly<br>educated, not<br>comparable to<br>general population      |

Information and results from studies regarding parental age and/or birth order.

<sup>a</sup>Results for hospital controls not shown.

\*Reporting was not complete or not clear.

AD=Alzheimer's disease

CDR=Clinical Dementia Rating Scale

CIDI=Composite International diagnostic interview

DSM=Diagnostic and Statistical Manual of Mental Disorders

ICD=International Classification of Diseases.

IMC=The initial information-memory-concentration.

MGAD=Major gene probability for Alzheimer's disease

NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association)

NINDS-AIREN=National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences

NS=Not statistically significant

SES=Socioeconomic status

SIDAM= Structured Interview for the diagnosis of Dementia of the Alzheimer type, Multi-infarct dementia and dementias of other etiology according to ICD-10 and DSM-III-R

## Season of birth

| Author               | Ref. | Outcome                                                    |                                                                                                                                  |                            | Statistical test                                                                                                                                              | Covariates accounted for in model or by matching                          | Exposure                                           | Results (by exposure)                                                                                                                                                                                                                                                                                     |                                                              | Key limitations                                                         |
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|                      |      | Type                                                       | Measurement/criteria                                                                                                             | Age; mean (SD; range)      |                                                                                                                                                               |                                                                           |                                                    | Unadjusted/crude model                                                                                                                                                                                                                                                                                    | Fully adjusted model                                         |                                                                         |
| Season of birth      |      |                                                            |                                                                                                                                  |                            |                                                                                                                                                               |                                                                           |                                                    |                                                                                                                                                                                                                                                                                                           |                                                              |                                                                         |
| Case-control studies |      |                                                            |                                                                                                                                  |                            |                                                                                                                                                               |                                                                           |                                                    |                                                                                                                                                                                                                                                                                                           |                                                              |                                                                         |
| Dysken               | 68   | Alzheimer's disease (autopsy proven)                       | Post-mortem brain specimens were examined for large numbers of neuritic plaques and neurofibrillary tangles                      | Not reported               | Chi-squared analysis: observed vs expected birth, individual quarter vs remaining quarters (yates correction) Edwards' procedure for estimating cyclic trends | -                                                                         | Season of birth (by quarter)                       | AD observed birth quarter vs expected. Chi-squared (df:3) 2.07 NS<br><br>Per birth quarter, Chi-squared (df:1): Jan-March: 1.03 NS<br>Apr-June: 0.51 NS<br>Jul-Sept: 1.03 NS<br>Oct-Dec: 0.20 NS<br><br>Edwards's method did not observe a peak period of AD births.<br><br>(subgroup results in table C) | -                                                            | -Not accounting for confounders, like birth years<br>-Limited reporting |
| Fratiglioni          | 61   | Alzheimer's disease                                        | MMSE screening, DSM III-R criteria with some modifications; mild, moderate or severe dementia according to CDR scale             | >75                        | ORs, Logistic regression                                                                                                                                      | Included in adjusted model: age, sex and education                        | Season of birth (birth in 1 <sup>st</sup> quarter) | 1 <sup>st</sup> quarter vs rest of the year RR 1.4 (0.8-2.2)                                                                                                                                                                                                                                              | 1 <sup>st</sup> quarter vs rest of the year RR 1.4 (0.9-2.3) | -                                                                       |
| Frazee               | 74   | Alzheimer's disease (clinical diagnosis or autopsy proven) | Cases listed as probable AD or AD verified by autopsy from the AD research centers of California database; time of diagnosis ≥65 | Not reported. At least >65 | Comparison of AD births per quarter/month vs expected births; chi-squared test                                                                                | Expected births were based on the specific birth years in the case sample | Season (by quarter) and month of birth             | Per quarter: chi-squared (2, n=1359)=0.26 NS<br><br>Disproportionate number of births in the first 4 months, chi-squared=3.90, p<0.05                                                                                                                                                                     | -                                                            | Limited reporting                                                       |

|           |    |                            |                                                                                                                |              |                                                                                                                                                          |                                                                                      |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |   |                                                                                               |
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| Henderson | 69 | Alzheimer's disease        | Possible or probable AD according to NINCDS-ADRDA criteria                                                     | Not reported | Chi-squared test; Roger's method for cyclic trends                                                                                                       | Frequency matched on: age and gender                                                 | Season of birth (per quarter)                                   | Per quarter: cases vs controls: chi-squared=1.48, p=0.69<br>Cases vs general population: chi-squared=1.51, p=0.68<br>Roger's test: chi-square:2.18 p=0.34 (monthly also NS)<br><br>(subgroup results in table C)                                                                                                                                                                                                                                             | - | -Limited reporting                                                                            |
| Koch      | 75 | Dementia (vascular and AD) | Dementia diagnosis from the psychogeriatric ward of the University clinic of Regensburg; between 1995 and 2004 | Not reported | Chi-squared test, circannual Cosinor models                                                                                                              | Births were normalized according to the mean birth year of the patient sample        | Season of birth (Dec-Feb, March-May, June-August, Sep-November) | No significant circannual variation in patient births P>0.05<br><br>Tendency towards higher mean birth frequencies in the fall for vascular dementia and winter for Alzheimer patients                                                                                                                                                                                                                                                                       | - | -Limited reporting<br>-Results/statistics insufficiently reported                             |
| Lawlor    | 72 | Alzheimer's disease        | NINCDS-ADRDA criteria for probable AD                                                                          | Not reported | Chi-squared test                                                                                                                                         | Matched for age                                                                      | Season of birth (first quarter)                                 | Percentages of first-quarter births<br>AD: 27%<br>Controls: 20.9%<br>Census-derived data: 25.1%<br>NS                                                                                                                                                                                                                                                                                                                                                        | - | -Very limited reporting (letter to the editor)<br>-Results/statistics insufficiently reported |
| Philpot   | 73 | Alzheimer's disease        | Probable AD according to NINCDS-ADRDA criteria                                                                 | Not reported | Chi-squared test for observed vs expected births. Roger's method for testing cyclic trends and Edwards' method for determining the peak quarter of birth | Age structure of the comparison sample was matched to the cases (by decade of birth) | Season of birth (per quarter)                                   | Quarterly variation of births compared to controls: chi-squared=6.35, p<0.1 p>0.05<br><br>Comparison with remaining quarters: (df=1)<br>January-March: chi-squared=5.67, p<0.02 75 observed/59.1 expected<br>April-June: chi-squared=1.79, p>0.1 52 observed/60.9 expected<br>July-September: chi-squared=0.003, p>0.9 60 observed/60.3 expected<br>October-December: chi-squared=1.83, p>0.1 52 observed/58.6 expected<br><br>(subgroup results in table C) | - | -Limited reporting                                                                            |

|           |    |                                                      |                                                                                                                                                                                                                              |                                                                                  |                                                                                                             |                                                                                             |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                |                         |
|-----------|----|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------|
| Prince    | 36 | Alzheimer's disease and other dementias (onset > 65) | DSM-III-R criteria for dementia including AD, multi-infarct dementia, mixed vascular and AD and amnesic syndrome; possible or probable AD according to NINCDS-ARDA criteria                                                  | 71-87                                                                            | Odds ratios; logistic regression for adjusted analysis                                                      | Included in model: age, sex, family history of dementia, premorbid IQ and area of residence | Season of birth                         | NS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | NS                                                                                                             | -Very limited reporting |
| Ptok 2001 | 70 | Alzheimer's disease                                  | ICD-10 or DSM-III-R diagnosis; CIDI and SIDAM interviews, thorough clinical examination                                                                                                                                      | AD 76.99 (9.66), co-morbid AD and depression 73.45 (9.58), controls 76.99 (9.66) | Chi-squared test, logistics regression to examine the effect of birth in the first three months of the year | Included in model: age, sex, ApoE                                                           | Season of birth (quarterly birth rates) | AD vs controls chi-squared: 2.99 (df=3) p=0.39<br><br>(subgroup results in table C)                                                                                                                                                                                                                                                                                                                                                                                                                                  | Birth in the first three months of the year had no effect on AD (in the adjusted logistic regression analyses) | -Limited reporting      |
| Tolppanen | 76 | Alzheimer's disease                                  | From the finish reimbursement register; all records of individuals eligible for higher reimbursement due to certain chronic diseases, including AD<br><br>Must be diagnosed following NINCDS-ADRD and DSM-IV criteria for AD | 34-105<br><br>For cases 80.1 (71)                                                | Conditional logistic regression                                                                             | Matched on: age (+/- 1 year), sex and region of residence                                   | Month and season of birth               | Jan = reference<br>Feb: OR 1.02 95%CI 0.98-1.06<br>Mar: OR 0.99 95%CI 0.95-1.03<br>Apr: OR 1.02 95%CI 0.98-1.07<br>May: OR 1.02 95%CI 0.98-1.06<br>Jun: OR 1.02 95%CI 0.98-1.06<br>Jul: OR 1.04 95%CI 1.00-1.08<br>Aug: OR 1.00 95%CI 0.97-1.04<br>Sep: OR 1.02 95%CI 0.98-1.06<br>Oct: OR 1.00 95%CI 0.96-1.04<br>Nov: OR 0.99 95%CI 0.95-1.04<br>Dec: OR 0.97 95%CI 0.93-1.01<br>p=0.09<br><br>Winter (nov-feb) Reference<br>Spring (march-may) 1.02 95% CI 0.99-1.04<br>Summer (june-august) 1.03 95%CI 1.00-1.05 | -Also included very young AD patients                                                                          |                         |

|        |    |                     |                                                              |              |                                                  |                                                                                                                                               |                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                        |                                                                 |
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|        |    |                     |                                                              |              |                                                  |                                                                                                                                               |                         | Autumn (sep-oct) 1.02<br>95%CI 0.99-1.04<br>P=0.13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                        |                                                                 |
| Vezina | 80 | Alzheimer's disease | NINCDS-ADRDA criteria for possible, probable and definite AD | Not reported | Chi-squared test for observed vs expected births | Included in adjusted model: birthyear (3-year periods)<br><br>In the comparison to the SOREP control group everyone was born in the SLSJ area | Season of birth (month) | Jan<br>RAMQ p=0.28<br>SOREP p=0.82<br>Feb<br>RAMQ p=0.07 (cases > controls)<br>SOREP p=0.22<br>Mar<br>RAMQ p=0.90<br>SOREP p=0.97<br>Apr<br>RAMQ p=0.54<br>SOREP p=0.74<br>May<br>RAMQ p=0.01 (cases < controls)<br>SOREP p=0.02 (cases < controls)<br>Jun<br>RAMQ p=0.44<br>SOREP p=0.26<br>Jul<br>RAMQ p=0.54<br>SOREP p=0.97<br>Aug<br>RAMQ p=0.47<br>SOREP p=0.70<br>Sep<br>RAMQ p=0.53<br>SOREP p=0.76<br>Oct<br>RAMQ p=0.24<br>SOREP p=0.13<br>Nov<br>RAMQ p=0.60<br>SOREP p=0.34<br>Dec<br>RAMQ p=0.92<br>SOREP p=0.90<br><br>chi2=10.96, df=11, p>0.10<br><br>Daily distributions: | P-values were similar for the adjusted and unadjusted analyses; not clearly reported if reported p-values were for the adjusted or unadjusted analyses | -Limited reporting<br>-Multiple testing<br>-Low number of cases |

|                |    |                     |                                                                                                                                                                                                                                                                                    |                                                           |                                                   |                                                                                                                                                                                                                                                                            |                                         |                                                                                                                                                                                                         |                                                                                                                                                                                                                                     |                                               |
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|                |    |                     |                                                                                                                                                                                                                                                                                    |                                                           |                                                   |                                                                                                                                                                                                                                                                            |                                         | The deficit of births in May remains significant, but also includes some days in June                                                                                                                   |                                                                                                                                                                                                                                     |                                               |
| Vitiello       | 71 | Alzheimer's disease | McKhann criteria                                                                                                                                                                                                                                                                   | Cases 67.4 (9.1; 42-87) at diagnosis. Controls 66.2 (8.3) | Chi-squared test; Edwards method for cyclic trend | No matching; age and gender were similar                                                                                                                                                                                                                                   | Season of birth (quarterly birth rates) | Quarterly distribution: chi-squared=3.6 (df 3) p=0.31<br>Monthly distribution: chi-squared=11.9 (df 11) p=0.37<br><br>No significant cyclic trend (Edwards method)<br><br>(subgroup results in table C) | -                                                                                                                                                                                                                                   | -Limited reporting                            |
| Cohort studies |    |                     |                                                                                                                                                                                                                                                                                    |                                                           |                                                   |                                                                                                                                                                                                                                                                            |                                         |                                                                                                                                                                                                         |                                                                                                                                                                                                                                     |                                               |
| Ding           | 78 | Dementia            | Combination of self-report or report by family member (with a trained interviewer) and checked by doctors with more than 5-year clinical experience; ICD-10-AM codes: F00 AD, F01 vascular dementia, F02 dementia in other diseases classified elsewhere, F03 unspecified dementia | 69.68 (SD 7.24 >60)<br><br>Dementia cases, 75.69 (8.29)   | Logistic regression                               | Adjusted for: age, gender, education and annual household income per capita                                                                                                                                                                                                | Season of birth                         | -                                                                                                                                                                                                       | Spring (Mar, Apr, May) OR 0.85 95%CI 0.72-1.01 p=0.062<br>Summer Reference<br>Autumn (Sep, Oct, Nov) OR 0.89 95%CI 0.76-1.05 p=0.165<br>Winter (Dec, Jan, Feb) OR 0.76 95%CI 0.65-0.90 p=0.001<br><br>(subgroup results in table C) | -Limited reporting                            |
| Doblhamer      | 77 | Dementia            | ICD-10 codes: G30, G31.0, G31.82, G23.1, F00, F01, F02, F03, F05<br><br>Individuals were followed over a one year period.<br><br>Those with a verified second occurrence in the following 3-years were considered valid dementia cases                                             | >65                                                       | Logistic regression                               | Crude model: adjusted for age (5-year groups) and gender<br><br>Included in fully adjusted model: adjusted for age (5-year groups), gender, diabetes mellitus, hypertension, ischemic heart disease, cerebrovascular diseases, hypercholesterolemia, arterial fibrillation | Season of birth                         | Winter (Dec, Jan, Feb) OR 0.93 p=0.004<br>Spring (Mar, Apr, May) OR 0.96 p=0.167<br>Summer (Jun, Jul, Aug) reference<br>fall (Sep, Oct, Nov) OR 0.95 p=0.051                                            | Winter: OR 0.93, p=0.004<br>Spring: OR 0.95, p=0.077<br>Summer reference<br>Fall: OR 0.95, p=0.070                                                                                                                                  | -Limited reporting<br>-Short follow-up period |

|          |    |                                         |                                                                                 |              |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                          |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                    |
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| Hsu      | 81 | Alzheimer's disease                     | ICD-9 code: 331.0; insurer's registry data.                                     | Not reported | Walter & Elwood's (W&E) test to estimate the within-year fluctuations with 12-month periodicity | -                                                                                                                                                                                                                                                                                                                                                                                                        | Month of birth                                | Jan RR 1.079<br>Feb RR 1.071<br>Mar RR 0.987<br>Apr RR 0.937<br>May RR 0.967<br>Jun RR 0.940<br>Jul RR 0.961<br>Aug RR 0.931<br>Sep RR 1.073<br>Oct RR 1.004<br>Nov RR 1.016<br>Dec RR 1.011<br><br>P (W&E <0.001)<br><br>(subgroup results in table C)                                                                                                                                                                                                                                                                                                                                                                                            | -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -Limited reporting |
| Mooldijk | 79 | All-cause dementia; Alzheimer's disease | Consensus panel (led by neurologist) using DSM-III-R and NINCDS-ADRDA criteria. | 64.8 (9.6)   | Cox-proportional hazard models                                                                  | Model 1: adjusted for age and sex<br>Model 2: additionally adjusted for educational level<br>Model 3: additionally adjusted for ethnicity, income, use of alcohol, smoking, body mass index, blood pressure, total and high-density lipoprotein cholesterol, APOE genotype, history of diabetes, history of stroke, history of coronary heart disease, history of heart failure and depressive symptoms. | Season and month of birth; severity of winter | Model 1<br>All-cause dementia<br>Winter (Dec, Jan, Feb)<br>HR 1.15 (95%CI 1.01-1.31)<br>Spring (Mar, Apr, May)<br>HR 1.12 (95%CI 0.98-1.28)<br>Summer (Jun, Jul, Aug)<br>Reference<br>Fall (Sep, Oct, Nov)<br>HR 1.17 (95%CI 1.03-1.33)<br><br>Normal winter<br>HR 1.10 (95%CI 0.95-1.26)<br>Cold winter<br>HR 1.34 (95%CI 1.05-1.71)<br>Very cold winter<br>HR 1.35 (95%CI 0.99-1.84)<br>Summer<br>Reference<br><br>Alzheimer's disease<br>Winter (Dec, Jan, Feb)<br>HR 1.23 (95%CI 1.06-1.43)<br>Spring (Mar, Apr, May)<br>HR 1.14 (95%CI 0.98-1.33)<br>Summer (Jun, Jul, Aug)<br>Reference<br>Fall (Sep, Oct, Nov)<br>HR 1.15 (95%CI 0.99-1.35) | Model 3<br>All-cause dementia<br>Winter (Dec, Jan, Feb)<br>HR 1.13 (95%CI 0.99-1.29)<br>Spring (Mar, Apr, May)<br>HR 1.10 (95%CI 0.96-1.26)<br>Summer (Jun, Jul, Aug)<br>Reference<br>Fall (Sep, Oct, Nov)<br>HR 1.10 (95%CI 0.96-1.26)<br><br>Normal winter<br>HR 1.10 (95%CI 0.95-1.26)<br>Cold winter<br>HR 1.29 (95%CI 1.01-1.65)<br>Very cold winter<br>HR 1.34 (95%CI 0.98-1.83)<br>Summer<br>Reference<br><br>Alzheimer's disease<br>Winter (Dec, Jan, Feb)<br>HR 1.20 (95%CI 1.03-1.40)<br>Spring (Mar, Apr, May)<br>HR 1.13 (95%CI 0.96-1.32)<br>Summer (Jun, Jul, Aug)<br>Reference<br>Fall (Sep, Oct, Nov)<br>HR 1.08 (95%CI 0.92-1.26) | -                  |



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Information and results from studies regarding season of birth.

AD=Alzheimer's disease

CDR=Clinical Dementia Rating Scale

CIDI=Composite International diagnostic interview

DSM=Diagnostic and Statistical Manual of Mental Disorders

ICD=International Classification of Diseases.

NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association)

NS=Not statistically significant

SIDAM= Structured Interview for the diagnosis of Dementia of the Alzheimer type, Multi-infarct dementia and dementias of other etiology according to ICD-10 and DSM-III-R

## Place of birth

| Author               | Ref. | Outcome                                      |                                                                                                                   |                                      | Statistical test                                                                                                                         | Covariates accounted for in model or by matching                                                                       | Exposure                                                  | Results (by exposure)                                                                                                                                                                                                                                                                                      |                      | Key limitations                                                                                         |
|----------------------|------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------------------------------------------------------------------------------------|
|                      |      | Type                                         | Measurement/criteria                                                                                              | Age; mean (SD; range)                |                                                                                                                                          |                                                                                                                        |                                                           | Unadjusted/crude model                                                                                                                                                                                                                                                                                     | Fully adjusted model |                                                                                                         |
| Place of birth       |      |                                              |                                                                                                                   |                                      |                                                                                                                                          |                                                                                                                        |                                                           |                                                                                                                                                                                                                                                                                                            |                      |                                                                                                         |
| Case-control studies |      |                                              |                                                                                                                   |                                      |                                                                                                                                          |                                                                                                                        |                                                           |                                                                                                                                                                                                                                                                                                            |                      |                                                                                                         |
| Baker                | 83   | Alzheimer's disease                          | All individuals with cognitive impairment were evaluated; diagnosis were standardized with McKhann criteria       | Not reported; most between 60 and 90 | Conditional logistic regression                                                                                                          | Matched on: age (within 5 years), sex, race marital status, status at time of surrogate interview (case alive or dead) | Place of birth (rural vs urban ?)*                        | OR 16.00 (1.91-*)<br><br>*Not meaningful due to small sample size                                                                                                                                                                                                                                          | -                    | -Multiple testing<br>-Small sample                                                                      |
| Emard                | 90   | Alzheimer's disease                          | NINCDS-ADRDA criteria for probable or definite AD cases                                                           | Not reported                         | Multivariate analysis, factor analysis of correspondences and differences in residential and municipal geochemical concentrations (DRMC) | -                                                                                                                      | Place of birth (geochemical composition)                  | No single geochemical element seems to be associated with the spatial distribution of cases<br><br>For Pb, Mn and Fe there were significantly (p<0.05) more cases with higher concentrations at their birth place than the average municipal concentration than there were cases with lower concentrations | -                    | -No actual control group<br>-Limited reporting<br>-No direct comparison with geochemical concentrations |
| Forster              | 48   | Presenile Alzheimer' disease (diagnosis <65) | Hospital cases notes were studied; DSM-III-R criteria for dementia, NINCDS-ADRDA criteria for Alzheimer's disease | Not reported; diagnoses <65          | OR's calculated with McNemar's test (taking matching into account)                                                                       | Matched on: age and sex                                                                                                | Place of birth (Aluminum concentration in drinking water) | Mean aluminum concentration at birth (n=160) (microgram/l)<br><50 1.3 95%CI 0.61-2.68<br>p=NS<br>>50 0.8 95%CI 0.37-1.64<br>p=NS<br>>99 0.8 95%CI 0.42-1.71<br>p=NS<br>>149 1.1 95%CI 0.38-3.35<br>p=NS<br><br>(subgroup results in table C)                                                               | -                    | -Multiple testing<br>-Only included early onset AD                                                      |

|         |    |                                                   |                                                                                                                                                                                                                              |              |                                                                                                                                    |                                       |                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                    |
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| Frecker | 89 | Dementia as a cause of death (death records)      | 1985 and 1986 death certificates were individually scanned for cause of death; dementia was defined by five possible categories: AD, chronic/organic brain syndrome, dementia, senile dementia/senile confusion, or senility | >70          | Calculated difference in proportions with confidence intervals; Fleiss correction factor was used for proportions smaller than 0.1 | Mortality rates were adjusted for age | Place of birth (drinking water quality)                  | Newfoundland population: -<br><br>Two birth regions (03 and 07) had high dementia mortality rates (mean standardized rates, 56.5 and 54.4/100 000), Whole population 34 and 27/100 000 (1985 and 1986)<br>03=isolated region on south west coast<br>07=includes Bonavista bay and the North shore of Trinity bay<br><br>Bonavista bay:<br>1985 15 deaths from north (17.2% of all deaths in that area)<br>9 from central and south (6.3% from that area) 95% CI 1.1-20.7 for proportion<br><br>1986: 12 deaths (14.3%), 4 (2.9%) 95%CI 2.5-20.4 for proportion<br><br>In the Newtown area high incidence of dementia death coincided with the lowest pH, highest concentration of aluminum and highest water color measurement in drinking water; two other areas also had higher measures but no corresponding dementia increase | -Limited reporting<br>-No direct associations measured with drinking water quality |
| Jean    | 82 | Alzheimer's disease (Clinical and autopsy proven) | Possible, probable or definite AD according to NINCDS/ADRDA criteria; definite cases were determined with autopsy                                                                                                            | Not reported | Exact probability test                                                                                                             | -                                     | Place of birth (rural and urban vs reference population) | Rural vs reference population OR=1.29 (p<0.01)<br>Urban vs reference population OR=0.84 (p<0.01)<br><br>(subgroup results in table C)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -Limited reporting<br>-No correction for year of birth or other variables          |

|                       |    |                                                      |                                                                                                                                                                                                                                                                                                                          |                                                                                                                                       |                                                                                         |                                                                                                                                                                                                                                                                                         |                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                               |                                          |
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| Prince                | 36 | Alzheimer's disease and other dementias (onset > 65) | DSM-III-R criteria for dementia including AD, multi-infarct dementia, mixed vascular and AD and amnesic syndrome; possible or probable AD according to NINCDS-ARDA criteria                                                                                                                                              | 71-87                                                                                                                                 | Odds ratios; logistic regression for adjusted analysis                                  | Included in model: age, sex, family history of dementia, premorbid IQ and area of residence                                                                                                                                                                                             | Place of birth (area of residence from birth to age 15; rural vs urban) | NS                                                                                                                                                                                                                                                                                                                                                                                                             | -                                                                                                                                                                                                                                                                                                                                                                                                             | -Very limited reporting                  |
| <i>Cohort studies</i> |    |                                                      |                                                                                                                                                                                                                                                                                                                          |                                                                                                                                       |                                                                                         |                                                                                                                                                                                                                                                                                         |                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                               |                                          |
| Gilsanz 2017          | 85 | Dementia                                             | <p>Dementia diagnosis was ascertained from records from a health care delivery system (KPNC) (follow-up from Jan 1996 – Oct 2015)</p> <p>Using ICD-9 codes: AD 331.0, vascular dementia 290.4x, other/nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.2x, 294.8)</p> <p>Mean follow-up time was 11.61 (6.24)</p> | Age in 1996 (start of follow-up) cases 71.18 (2.72), controls 71.14 (2.72)                                                            | Cox proportional hazards models with age as the time scale; cumulative risk of dementia | <p>Included in crude model: age and sex</p> <p>Included in fully adjusted model: age, sex, race, education, midlife (BMI, smoking duration, hypertension) and late life (diabetes, hypertension, heart failure, acute myocardial infarction and stroke) cardiovascular risk factors</p> | Place of birth (in high stroke mortality state)                         | <p>Age adjusted dementia incidence rate (per 1000 person years)</p> <p>Outside high-stroke: 15.54 95%CI 14.42-16.66</p> <p>Inside high-stroke: 23.56 95%CI 20.46-26.67</p> <p>HR 1.54 95%CI 1.39-1.71</p> <p>(subgroup results in table C)</p>                                                                                                                                                                 | Overall HR 1.27 95%CI 1.11-1.44<br>(subgroup results in table C)                                                                                                                                                                                                                                                                                                                                              | -All participants migrated to California |
| Gilsanz 2019          | 88 | Dementia                                             | <p>Dementia diagnosis was ascertained from records from a health care delivery system (KPNC) (follow-up from Jan 1996 – Oct 2015)</p> <p>Using ICD-9 codes: AD 331.0, vascular dementia 290.4x, other/nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.2x, 294.8)</p>                                             | Age in 1996 (start of follow-up) White cases 71.5 (2.8), controls 71.2 (2.7); African Americans cases 70.9 (2.8), controls 71.4 (2.8) | Cox proportional hazards models with age as the time scale; cumulative risk of dementia | <p>Included in crude model: age, sex, education</p> <p>Fully adjusted model: further adjusted for midlife vascular risk factors (BMI and high blood pressure) and late-life vascular risk factors (stroke and diabetes)</p>                                                             | Place of birth in high infant mortality rate areas (IMR; in quartiles)  | <p>White:</p> <p>Q1 (lowest IMR) reference</p> <p>Q2: HR 1.03 95%CI 0.89-1.19</p> <p>Q3: HR 1.20 95%CI 1.00-1.45</p> <p>Q4 (highest IMR): HR 1.06, 95%CI = 0.85-1.32</p> <p>African-American:</p> <p>Q1 (lowest IMR) reference</p> <p>Q2: HR 1.03 95%CI 0.83-1.28</p> <p>Q3: HR 0.92 95%CI 0.64-1.33</p> <p>Q4 (Highest IMR) : HR 1.35 95%CI 0.97-1.88</p> <p>Inside vs outside highest quartile IMR state</p> | <p>White:</p> <p>Q1 (lowest IMR) reference</p> <p>Q2: HR 1.03 95%CI 0.89-1.18</p> <p>Q3: HR 1.20 95%CI 1.00-1.45</p> <p>Q4 (highest IMR): HR 1.07 95%CI 0.86-1.34</p> <p>African-American:</p> <p>Q1 (lowest IMR) reference</p> <p>Q2: HR 1.08, 95%CI 0.87-1.35</p> <p>Q3: HR 0.96, 95%CI 0.67-1.40</p> <p>Q4 (highest IMR) : HR 1.44 95%CI 1.03-2.01</p> <p>Inside vs outside highest quartile IMR state</p> | -All participants migrated to California |

|         |    |                                                                               |                                                                                                                                                                                  |                          |                                                                                            |                                                                                                                                      |                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                    |
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|         |    |                                                                               |                                                                                                                                                                                  |                          |                                                                                            |                                                                                                                                      |                                                     | White:<br>HR 1.01, 95%CI 0.84-1.22<br>African-American:<br>HR = 1.35, 95%CI = 0.99-1.84                                                                                                                                                                                                                                                                                                                                                                      | White:<br>Inside: HR 1.03, 95%CI 0.85-1.24<br>African-American:<br>Inside: HR 1.40, 95%CI 1.02-1.91                                                                                                                                                                                                                                                                                                                                                      |                                                                                    |
| Glymour | 86 | All cause dementia or Alzheimer's disease as a cause of death (death records) | Mortality records were obtained from the National Center for Health Statistics multiple cause of death files. AD (ICD-10 G30), all cause dementia including AD (F00-F03, G30)    | 65-89 (in the year 2000) | Mortality rates; logistic regression                                                       | Included in crude model: Age, age-squared and sex<br><br>Fully-adjusted model: additionally adjusted for adult stroke belt residence | Place of birth (Stroke belt vs outside stroke belt) | All-cause dementia:<br>White:<br>OR 1.23 95%CI 1.21-1.25<br><br>African-American:<br>OR 1.25 95%CI 1.20-1.30<br><br>AD:<br>White:<br>OR 1.30 95%CI 1.27-1.33<br><br>African-American:<br>OR 1.28 95%CI 1.19-1.36<br><br>(subgroup results in table C)                                                                                                                                                                                                        | All-cause dementia:<br>White:<br>OR 1.19 95%CI 1.16-1.22<br><br>African-American:<br>1.29 95%CI 1.24-1.35<br><br>AD:<br>Patterns nearly identical to those for all-cause dementia                                                                                                                                                                                                                                                                        | -Limited reporting<br>-Cause of death on death certificates is not always accurate |
| Guaita  | 92 | Dementia and dementia subtypes (Alzheimer's disease and Vascular dementia)    | Geriatrician used DSM IV-TR criteria for dementia<br><br>AD: NINCDS-ADRDA criteria for probable, possible and definite diagnoses<br>Vascular dementia (VD): NINDS-AIREN criteria | 71.69 (70-74)            | Pearson's chi-squared test/fisher's exact test, likelihood ratio test, logistic regression | Included in fully adjusted model: gender, birth year, marital status, primary lifetime occupation, years of education                | Place of birth (location in Italy)                  | Crude prevalence<br>Dementia<br>North-western Italy: 2.3 95%CI 1.5-3.5<br>North-eastern Italy: 1.4 95%CI 0.2-4.9<br>Central Italy: 5.0 95%CI 0.1-24.9<br>Southern Italy: 9.4 95%CI 4.6-16.7<br>Italian islands: 6.3 95%CI 1.7-15.2<br>p=0.001<br><br>AD<br>North-western Italy: 0.9 95%CI 0.4-1.8<br>North-eastern Italy: 0.0 95%CI 0.0-2.5<br>Central Italy: 5.0 95%CI 0.1-24.9<br>Southern Italy: 1.9 95%CI 0.2-6.6<br>Italian islands: 4.7 95%CI 1.0-13.1 | Mutually adjusted prevalence<br>Dementia<br>North-western Italy: 2.2 95%CI 1.4-3.4<br>North-eastern Italy: 1.1 95%CI 0.3-4.6<br>Central Italy: 4.9 95%CI 0.7-29.0<br>Southern Italy: 2.2 95%CI 1.4-3.4<br>Italian islands: 5.4 95%CI 2.1-15.4<br>p>0.900<br><br>Southern Italy vs north-western Italy OR 4.06 95%CI 1.76-9.34 p=0.001<br><br>AD<br>North-western Italy: 0.6 95%CI 0.2-1.4<br>North-eastern Italy: -<br>Central Italy: 3.7 95%CI 0.4-26.1 | -Low number of participants born in certain subareas                               |

|          |    |                                                          |                                                                                                                                                                                                                                               |                                 |                     |                                                                                                                                                                                                                                                       |                                      |                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                    |   |
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|          |    |                                                          |                                                                                                                                                                                                                                               |                                 |                     |                                                                                                                                                                                                                                                       |                                      | <p>p=0.017</p> <p>VD</p> <p>North-western Italy: 1.1 95%CI 0.5-1.9</p> <p>North-eastern Italy: 0.7 95%CI 0.0-3.8</p> <p>Central Italy: 0.0 95%CI 0.0-16.8</p> <p>Southern Italy: 5.7 95%CI 2.1-11.9</p> <p>Italian islands: 1.6 95%CI 0.0-8.4</p> <p>p=0.020</p>       | <p>Southern Italy: 0.8 95%CI 0.2-4.2</p> <p>Italian islands: 2.4 95%CI 0.6-9.0</p> <p>p=0.624</p> <p>VD</p> <p>North-western Italy: 1.6 95%CI 0.3-1.5</p> <p>North-eastern Italy: 0.4 95%CI 0.1-3.2</p> <p>Central Italy: -</p> <p>Southern Italy: 3.7 95%CI 1.4-9.5</p> <p>Italian islands: 1.1 95%CI 0.1-8.3</p> <p>p&gt;0.900</p> <p>Southern Italy vs north-western Italy OR 6.36 95%CI 1.98-20.43 p=0.002</p> |   |
| Scazufca | 84 | Dementia                                                 | Harmonized one-phased dementia diagnostic procedure developed by the 10/66 Dementia Research Group and validated for use in population-based studies of LAMIC; diagnosis following DSM-IV criteria                                            | 72.2 (6.3)                      | Logistic regression | <p>Included in crude model: age and gender</p> <p>Included in fully adjusted model: literacy, head circumference, leg length, occupation, income, smoking, diabetes, hypertension, age and gender</p>                                                 | Place of birth (city, town or rural) | <p>City: prevalence = 2.7; reference</p> <p>Town: prevalence = 3.9; OR 1.78 95%CI 0.68-4.66</p> <p>Rural: prevalence = 5.8; OR 2.22 95%CI 0.94-5.24</p> <p>p-value for linear trend=0.04 (likelihood ratio test)</p>                                                   | <p>City: reference</p> <p>Town: OR 1.22 95%CI 0.45-3.32</p> <p>Rural: OR 1.23 95%CI 0.50-3.05</p> <p>p-value for linear trend=0.70</p>                                                                                                                                                                                                                                                                             | - |
| Topping  | 87 | Mortality from all-cause dementia or Alzheimer's disease | Mortality status was obtained from yearly linkage with the Master Death Files of the Social Security Administration. Cause of death information was searched in the National Death Index and based on ICD codes. Follow-up from 1995 to 2011. | 63.32 (4.53; 55-72) at baseline | Logistic regression | <p>Crude model: sex, age and age squared</p> <p>Fully adjusted model: additionally adjusted for educational attainment and self-rated health</p> <p>All models were modelled with and without adult stroke belt residence included and separately</p> | Place of birth (stroke belt)         | <p>All cause dementia mortality</p> <p>White population OR 1.13 95%CI 1.07-1.20</p> <p>Non-white population OR 1.24 95%CI 1.01-1.52</p> <p>Alzheimer's disease</p> <p>White population OR 1.21 95%CI 1.04-1.41</p> <p>Non-white population OR 0.90 95%CI 0.46-1.76</p> | <p>All cause dementia mortality</p> <p>White population OR 1.08 95%CI 1.02-1.15</p> <p>Non-white population OR 1.14 95%CI 0.92-1.41</p> <p>Alzheimer's disease</p> <p>White population OR 1.20 95%CI 1.02-1.40</p> <p>Non-white population OR 0.91 95%CI 0.46-1.79</p>                                                                                                                                             | - |

|        |    |                     |                       |            | for the white and non-white population |                                                                                                             | <i>Including adult stroke belt residence:</i>                                                                                                                        | <i>Including adult stroke belt residence:</i>                                                                                  |                                |
|--------|----|---------------------|-----------------------|------------|----------------------------------------|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
|        |    |                     |                       |            |                                        |                                                                                                             | All cause dementia mortality<br>White population<br>OR 1.03 95%CI 0.96-1.12<br>Non-white population<br>OR 1.12 95%CI 0.88-1.45                                       | All cause dementia mortality<br>White population<br>OR 0.97 95%CI 0.90-1.05<br>Non-white population<br>OR 1.05 95%CI 0.81-1.35 |                                |
|        |    |                     |                       |            |                                        |                                                                                                             | Alzheimer's disease<br>White population<br>OR 1.15 95%CI 0.94-1.40<br>Non-white population<br>OR 0.85 95%CI 0.38-1.90                                                | Alzheimer's disease<br>White population<br>OR 1.16 95%CI 0.95-1.42<br>Non-white population<br>OR 0.85 95%CI 0.38-1.92          |                                |
| Wilson | 91 | Alzheimer's disease | NINCDS-ADRDA criteria | 75.0 (7.0) | Proportional hazards model             | Included in crude model:<br>age and sex<br><br>Fully adjusted model:<br>additionally adjusted for education | Place of birth<br>(county SES level)<br><br>RR of incident AD associated with county socioeconomic level (per 1-unit increase in SES)<br><br>RR 1.36 95%CI 0.94-1.97 | RR 1.35, 95%CI 0.93-1.96                                                                                                       | -Population not representative |

Information and results from studies regarding place of birth.

\*Reporting was not complete or not clear.

AD=Alzheimer's disease

DSM=Diagnostic and Statistical Manual of Mental Disorders

ICD=International Classification of Diseases.

NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association)

NINDS-AIREN=National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences

NS=Not statistically significant

SES=Socioeconomic status

## Other factors

| Author               | Ref. | Outcome                                    |                                                                                                                                                                                               |                                                     | Statistical test                                                 | Covariates accounted for in model or by matching | Exposure                                                                                                  | Results (by exposure)                                                                                                                                                                                                                                                                                                     |                      | Key limitations                                                  |
|----------------------|------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------------------------------------------------------------|
|                      |      | Type                                       | Measurement/criteria                                                                                                                                                                          | Age; mean (SD; range)                               |                                                                  |                                                  |                                                                                                           | Unadjusted/crude model                                                                                                                                                                                                                                                                                                    | Fully adjusted model |                                                                  |
| Other factors        |      |                                            |                                                                                                                                                                                               |                                                     |                                                                  |                                                  |                                                                                                           |                                                                                                                                                                                                                                                                                                                           |                      |                                                                  |
| Case-control studies |      |                                            |                                                                                                                                                                                               |                                                     |                                                                  |                                                  |                                                                                                           |                                                                                                                                                                                                                                                                                                                           |                      |                                                                  |
| Jiang                | 97   | Dementia                                   | Self-report of significant memory impairment or dementia. In subjects with dementia, there was an additional query about the type. For some patients, information was provided by caregivers. | Men: 82.8 (1.1; 65-97)<br>Women: 84.5 (1.0; 65-104) | Two-way ANOVA and Turkey post hoc test for pairwise comparisons. | Sex was accounted for in the models              | Right hand second to fourth finger length ratio as an indication of prenatal sex hormone exposure (2D:4D) | Men: p=0.57<br><br>Women: p=0.006<br>Right hand 2D:4D higher in those with dementia                                                                                                                                                                                                                                       |                      | -Self-reported dementia measure<br>-Indirect measure of exposure |
| Vladeanu             | 96   | Alzheimer's disease                        | Diagnosed according to the NINCDS-ADRDA and DSM-IV-TR criteria by a multidisciplinary team of a consultant psychiatrist, clinical psychologist and dementia nurse specialist                  | Cases 78.3<br>controls 75.6                         | MANOVA and 2x2 independent measures analyses of variance         | Matched on: age and years of education           | The second to fourth finger length ratio as an indication of prenatal sex hormone exposure                | Group main effect/MANOVA: NS<br><br>Mean 2D:4D ratio<br>Men<br>Left hand: Cases: 1.03<br>Controls: 0.96 (0.02)<br>p<0.001<br><br>Women<br>Left hand: Cases: 0.97 (0.03)<br>vs Controls: 1.03 (0.04)<br>p=0.004<br><br>Similar results for mean (left and right hand) ratios. No significant results for right hand ratios | -                    | -Indirect measure of exposure<br>-Small sample                   |
| Cohort studies       |      |                                            |                                                                                                                                                                                               |                                                     |                                                                  |                                                  |                                                                                                           |                                                                                                                                                                                                                                                                                                                           |                      |                                                                  |
| Cocoros              | 93   | Dementia of any type and specific types of | Registry data, diagnostic ICD codes, eight and tenth revisions                                                                                                                                | Followed from age 62 until max                      | Poisson regression; incidence rate ratios (IRR)                  | Included in crude model: sex                     | Prenatal 1918 influenza pandemic exposure                                                                 | All ages: IRR 1.01 95%CI 0.99-1.04<br><br>Per type                                                                                                                                                                                                                                                                        | -                    | -Indirect measure of exposure<br>-Healthy survivor bias          |



|      |    |                                                                                     |                                                                                                                                                                                                     |                                                                              |                                                                                                                                                                                                           |                                                                                                                                     |                                                                                                              |                                                                                                                                                                                                  |                                                                         |                                                                                                                                                                                                                                |
|------|----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |    | dementia (AD, vascular dementia, other dementia)                                    | Danish National Patient Registry (DNPR) and the Psychiatric Central Research Registry (PCRR) between January 1 1977 and November 30 2013                                                            | their 92th birthday                                                          |                                                                                                                                                                                                           | They Included participants born before and conceived after the influenza pandemic to account for age                                |                                                                                                              | AD IRR 0.97 (0.93-1.01)<br>vascular dementia: IRR 1.04<br>95%CI 0.98-1.10<br>other dementia: IRR 1.03<br>95%CI 1.00-1.06<br><br>(subgroup results in table C)                                    |                                                                         |                                                                                                                                                                                                                                |
| Kang | 94 | Dementia                                                                            | The Clinical Dementia Rating CDR scale was administered in all subjects; dementia was diagnosed according to the DSM-5                                                                              | Pre-famine: 56.48(1.23),<br>famine: 53.42(1.13),<br>post-famine: 50.50(1.20) | Chi-squared test or Fisher's exact test to analyze the differences among the groups                                                                                                                       | -                                                                                                                                   | Prenatal famine exposure                                                                                     | Famine vs post-famine: 0.72% vs 0.27%, p=0.0331<br>Famine vs pre-famine: 0.72% vs 0.67%, p=0.8733<br><br>(subgroup results in table C)                                                           | -                                                                       | -No correction for age<br>-Participants were relatively young at outcome assessment                                                                                                                                            |
| Lenz | 95 | Dementia or Alzheimer's disease as cause of death (national normalized death rates) | National point estimates for deaths (adjusted for the population size) in 2012, from the Global Health Estimates summary tables were used (WHO 2014)                                                | Not reported and not relevant; looked at death rate irrespective of age      | Pearson correlation; not normally distributed data were transformed into rankit normal scores<br><br>They adjusted p-values for multiple hypothesis testing with the false discovery rate (FDR) procedure | -                                                                                                                                   | The second to fourth finger length ratio as an indication of prenatal sex hormone exposure (2D:4D)           | Cross-national correlations for men:<br>r= -0.59<br>p= 0.0032<br>p(FDR)= 0.0361<br><br>For women the results showed the same correlations as in men (not shown)                                  | -                                                                       | -Comparison across nations not across individuals, very crude analysis<br>-Self-reported measurements from different population than population at risk for dying of dementia.<br>-Not accounting for other causes/confounding |
| Luo  | 98 | Dementia (onset >60 years)                                                          | Clinical diagnosis by the research team, from the Swedish National Register or from the prescribed drug register as a proxy for dementia diagnosis. Using DSM-III-R or DSM-IV criteria or ICD codes | >60                                                                          | Logistic regression and cox proportional hazard regression by sex                                                                                                                                         | Crude model: birth year<br><br>Fully adjusted model: birth year, education, exercise, vascular risk, and postnatal hormone exposure | Presumed differential prenatal hormones exposure by comparing same-sex and opposite-sex dizygotic twin pairs | Logistic regression Opposite-sex compared to same-sex Women OR 0.37 95%CI 0.25-0.54 p<0.0001<br>Men OR 0.47 95%CI 0.31-0.70 p<0.0001<br><br>Cox regression Women HR 0.83 95%CI 0.65-1.06 p=0.141 | Similar results<br><br>Interaction between twin type and APOE e4 was NS | -All participants were twins (less generalizable)<br>-Indirect measure of prenatal hormone environment                                                                                                                         |

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Men  
HR 0.96 95%CI 0.74-1.25  
p=0.751

Diagnosis after 70  
Women  
HR 0.64 95%CI 0.48-0.87  
p=0.004  
Men NS

Diagnosis after 80  
Women  
HR 0.38 95%CI 0.21-0.68  
p=0.001  
Men NS

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Information and results from studies regarding other factors.

AD=Alzheimer's disease

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NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association)

NS=Not significant

## Birth characteristics

| Author         | Ref. | Outcome                                         |                                                                                                                                                                     |                                                             | Statistical test                                                              | Covariates accounted for in model or by matching                                                                                                                                                              | Exposure                                       | Results (by exposure)                                                                                                                                                       |                                                                                                                                     | Key limitations                                                                                                              |
|----------------|------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
|                |      | Type                                            | Measurement/criteria                                                                                                                                                | Age; mean (SD; range)                                       |                                                                               |                                                                                                                                                                                                               |                                                | Unadjusted/crude model                                                                                                                                                      | Fully adjusted model                                                                                                                |                                                                                                                              |
| Birth size     |      |                                                 |                                                                                                                                                                     |                                                             |                                                                               |                                                                                                                                                                                                               |                                                |                                                                                                                                                                             |                                                                                                                                     |                                                                                                                              |
| Cohort studies |      |                                                 |                                                                                                                                                                     |                                                             |                                                                               |                                                                                                                                                                                                               |                                                |                                                                                                                                                                             |                                                                                                                                     |                                                                                                                              |
| Matshusima     | 99   | Dementia                                        | Self-reported; ever diagnosed with dementia                                                                                                                         | Cases 65.0 (6.7), controls 63.3 (6.6) at outcome assessment | Regression with linear probability model (binary outcome)                     | Included in adjusted model: sex, birth year, birth before the end of WWII, residential municipality, educational attainment, household SES during childhood, smoking and owning a home with land in adulthood | Low birth weight - (including premature birth) |                                                                                                                                                                             | 0.024 (0.013)<br>R-squared: 0.04<br>NS                                                                                              | -Self-reported exposure and outcome<br>-Limited reporting<br>-Multiple testing<br>-Limited number of cases/small sample size |
| Mosing         | 65   | Dementia (clinical diagnosis or cause of death) | Register-based dementia diagnoses as well as date of first diagnosis were derived from the NPR and CDR. ICD 7-10 codes for AD, vascular dementia and other dementia | 74.3 (2.6; 55-88)                                           | Cox proportional hazard analysis; corrected for correlation within twin pairs | Included in fully-adjusted model: sex, year of birth (10 year interval), parity, age of mother, birth SES, education level                                                                                    | Birth weight                                   | BW (100g): HR=0.98, 95%CI=0.97-1.00, p=0.016<br>LBW: HR=1.19, 95%CI=1.04-1.36, p=0.011<br>BWGA: HR=0.92, 95%CI=0.86-0.99, p=0.017<br>SGA: HR=1.19, 95%CI=0.81-1.76, p=0.380 | BW (100g) 0.98 (0.97-0.99) p=0.004<br>LBW 1.22 (1.07-1.40) p=0.004<br>BWGA 0.91 (0.85-0.98) p=0.008<br>SGA 1.19 (0.80-1.76) p=0.420 | -Registry data might miss a lot of dementia diagnosis<br>-Only twins were included (population not representative)           |
|                |      |                                                 |                                                                                                                                                                     |                                                             |                                                                               |                                                                                                                                                                                                               | Head circumference at birth                    | HC (mm): HR 1.00, 95%CI 0.99-1.00, p=0.304<br>HCGA 0.97 95%CI 0.90—1.04, p=0.401<br>SHCGA 1.67 95%CI 1.15-2.41 p=0.007                                                      | HC (mm) 1.00 (0.99-1.00) 0.220<br>HCGA 0.97 (0.90-1.04) 0.415<br>SHCGA 1.65 (1.14-2.39) 0.008                                       |                                                                                                                              |
|                |      |                                                 |                                                                                                                                                                     |                                                             |                                                                               |                                                                                                                                                                                                               | Birth length                                   | BL (cm): HR=0.98, 95%CI=0.96-1.01, p=0.136<br>BLGA: HR=0.96, 95%CI=0.89-1.02, p=0.195<br>SBLGA: HR=1.40, 95%CI=0.99-1.98, p=0.058                                           | BL (cm) 0.98 (0.95-1.00) 0.073<br>BLGA 0.95 (0.89-1.02) 0.167<br>SBLGA 1.40 (0.98-1.98) 0.062                                       |                                                                                                                              |

|         |     |                                                      |                                               |                                                                   |                                                                                                        |                                                               |                 |                                                                                      |                                                                           |                                                                                              |
|---------|-----|------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|-----------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
|         |     |                                                      |                                               |                                                                   |                                                                                                        |                                                               | Gestational age | GA (weeks) 0.99 (0.96-1.02)<br>p=0.461<br>Preterm 0.96 (0.82-1.13)<br>p=0.652        | GA (weeks) 0.99 (0.96-1.02)<br>0.396<br>Preterm 0.97 (0.82-1.14)<br>0.729 |                                                                                              |
|         |     |                                                      |                                               |                                                                   |                                                                                                        |                                                               | Birth SES       | NS*                                                                                  |                                                                           |                                                                                              |
|         |     |                                                      |                                               |                                                                   |                                                                                                        |                                                               |                 | <i>(subgroup results in table C)</i>                                                 |                                                                           |                                                                                              |
| Syddall | 100 | Alzheimer's disease and dementia (as cause of death) | Death certificate according to ICD-9; AD: 297 | All ages (death certificates); separate analysis by age 65 and 75 | Cox proportional hazards model; hazard ratio presented per standard deviation increase in birth weight | Birth year was included in all cox proportional hazard models | Birth weight    | Only sex-specific results were presented<br><br><i>(subgroup results in table C)</i> | -                                                                         | -Limited reporting<br>-Only presented sex-specific analysis<br>-Low number of dementia cases |

Information and results from studies regarding birth characteristics.

\*Reporting was not complete or not clear.

AD=Alzheimer's disease

CDR=Clinical Dementia Rating Scale

ICD=International Classification of Diseases.

NPR=National patient registry

NS=Not significant

SES=Socioeconomic status

Table C – Subgroup results

Parental age and birth order

| Author                       | Ref. | Exposure     | Sex-specific analysis            | Other sub-group analyses |                                                                                                                               |                                                                                                                                                          |
|------------------------------|------|--------------|----------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |      |              | Description and statistical test | Results (by exposure)    | Description and statistical test                                                                                              | Results (by exposure)                                                                                                                                    |
| Parental Age and birth order |      |              |                                  |                          |                                                                                                                               |                                                                                                                                                          |
| Case-control studies         |      |              |                                  |                          |                                                                                                                               |                                                                                                                                                          |
| Bertram                      | 45   | Maternal age | -                                | -                        | Independent student's t-test; Low major AD gene probability (L) vs control                                                    | (L) mean(SD) 29.4(6.6) vs 28.0(6.8) p=NS<br>(H) mean(SD) 29.1(5.7) vs 28.0(6.8) P=NS                                                                     |
|                              |      | Paternal age |                                  |                          | High major AD gene probability (H) vs control                                                                                 | (L) mean(SD) 35.7 (8.1) vs 32.6 (6.8) p=0.04<br>(H) mean(SD) 31.3(6.9) vs 32.6(6.8) p=NS                                                                 |
| Clarnette                    | 46   | Maternal age | -                                | -                        | Means were reported for possible AD, probable AD and possible/probable AD with a family history of AD                         | Controls (spouses) mean 27.9 SE 0.57<br>Possible AD mean 28.1 SE 1.01<br>Probable AD mean 30.5 SE 0.92<br>AD with family history of AD mean 29.7 SE 1.25 |
|                              |      | Paternal age |                                  |                          |                                                                                                                               | Controls (spouses) mean 31.1 SE 0.73<br>Possible AD mean 31.9 SE 1.10<br>Probable AD mean 34.3 SE 1.17<br>AD with family history of AD mean 33.4 SE 1.35 |
| Corkin                       | 42   | Maternal age | -                                | -                        | Means reported for AD onset <65 or ≥65 years                                                                                  | Cases <65 years 27.5 (19-44)<br>≥65 years 28.2 (18-35)<br>Controls 27.4 (17-40)                                                                          |
|                              |      | Paternal age |                                  |                          |                                                                                                                               | <65 years 30.4 (21.50)<br>≥65 years 31.2 (25-42)<br>Controls 29.4 (18-39)                                                                                |
| English                      | 47   | Maternal age | -                                | -                        | Chi-square test for trend; 95% CIs for odds ratios calculated by Cornfields method; early (<65) and late (65+) onset AD cases | Distribution of early onset (<65) and late onset cases (65+) were very similar; values not reported                                                      |

|             |    |              |   |   |                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------|----|--------------|---|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Farrer 1991 | 33 | Maternal age | - | - | <p>Paired comparison t-test and conditional logistic regression (5- year age interval)</p> <p>Early onset (&lt;67.2) vs late onset (&gt;67.2)</p> <p>Family history (familial AD) vs no family history of AD (sporadic AD)</p> <p>Parental and maternal age were included in one model*</p> | <p>Late onset (&gt;67.2), mean maternal age, cases 27.0 controls 28.3, p=0.035</p> <p>Late onset, sporadic AD, mean maternal age, cases 26.5, controls 28.1, p=0.050</p> <p>Family history: no difference in mean maternal age</p> <p>Early onset (&lt;67.2) OR 1.07 95%CI 0.83-1.37</p> <p>Late onset OR 1.01 95%CI 0.82-1.25</p> <p>Early onset, familial AD, OR 1.30 95%CI 0.82-2.06</p> <p>Early onset, sporadic AD, OR 0.97 95%CI 0.72-1.31</p> <p>Late onset, familial AD, OR 1.18 95%CI 0.82-1.70</p> <p>Late onset, sporadic AD, OR 0.93 95%CI 0.71-1.21</p>                |
|             |    | Paternal age |   |   |                                                                                                                                                                                                                                                                                             | <p>Late onset (&gt;67.2), mean paternal age, cases 30.2 controls 31.5, p=0.003</p> <p>Late onset, sporadic AD, mean paternal age, cases 29.8 controls 32.0, p=0.019</p> <p>Family history: no difference in mean paternal age</p> <p>Early onset (&lt;67.2) OR 1.02 95%CI 0.81-1.29</p> <p>Late onset OR 0.80 95%CI 0.67-0.96 p=0.019</p> <p>Early onset, familial AD, OR 0.89 95%CI 0.55-1.42</p> <p>Early onset, sporadic AD, OR 1.07 95%CI 0.82-1.40</p> <p>Late onset, familial AD, OR 0.71 95%CI 0.51-0.99 p=0.045</p> <p>Late onset, sporadic AD, OR 0.85 95%CI 0.68-1.06</p> |
| Farrer 1997 | 59 | Maternal age | - | - | <p>Conditional logistic regression; grouped by combination of APOE genotype and two parental age categories (old vs young defined by de median of 28 and 31 for maternal and paternal age respectively)</p>                                                                                 | <p>E3/e3 OR 1.13 95%CI 0.82-1.56</p> <p>E2/e3 OR 2.26 95%CI 0.95-5.33</p> <p>E2/e4 OR 1.38 95%CI 0.36-5.25</p> <p>E3/e4 OR 1.62 95%CI 1.14-2.30</p> <p>E4/e4 OR 2.06 95%CI 0.72-5.88</p> <p>Least square mean, E3/e4 cases 29.5 controls 28.0 p=0.007 (adjusted for gender, age and year of birth)</p>                                                                                                                                                                                                                                                                              |
|             |    | Paternal age |   |   |                                                                                                                                                                                                                                                                                             | <p>E3/e3 OR 1.34 95%CI 0.98-1.84</p> <p>E2/e3 OR 1.16 95%CI 0.49-2.68</p> <p>E2/e4 OR 0.54 95%CI 0.12-2.32</p> <p>E3/e4 OR 1.79 95%CI 1.26-2.54</p> <p>E4/e4 OR 1.26 95%CI 0.47-3.41</p>                                                                                                                                                                                                                                                                                                                                                                                            |

|                       |    |                            |                                                                                                                                                                                                                                               |                                                                                                                                                                                              |                                                                                                               |                                                                                                                                                                                                                                                  |
|-----------------------|----|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                       |    |                            |                                                                                                                                                                                                                                               |                                                                                                                                                                                              |                                                                                                               | Least square mean, E3/e4 cases 33.3 controls 30.8<br>p<0.0001 (adjusted for gender, age and year of birth)                                                                                                                                       |
| Hofman                | 50 | Maternal age               | -                                                                                                                                                                                                                                             | -                                                                                                                                                                                            | Conditional logistic regression (matched design) for sporadic AD cases (without a family history of dementia) | ≤24 reference<br>25-29 RR 0.8 95%CI 0.4-1.7<br>30-34 RR 0.9 95%CI 0.4-1.9<br>35-39 RR 0.7 95%CI 0.3-1.9<br>40+ RR 0.9 95%CI 0.3-2.8<br>Difference in mean maternal age were similar for individuals with or without a family history of dementia |
|                       |    | Paternal age               |                                                                                                                                                                                                                                               |                                                                                                                                                                                              |                                                                                                               | ≤24 reference<br>25-29 RR 1.1 95%CI 0.4-2.8<br>30-34 RR 1.0 95%CI 0.4-2.6<br>35-39 RR 0.7 95%CI 0.2-2.2<br>40+ RR 0.8 95%CI 0.2-2.5<br>Difference in mean paternal age were similar for individuals with or without a family history of dementia |
|                       |    | Birth order                |                                                                                                                                                                                                                                               |                                                                                                                                                                                              |                                                                                                               | NS for individuals with an without a family history of dementia                                                                                                                                                                                  |
| Whalley 1995          | 34 | Maternal age               | Conditional logistic regression; matched on: sex, birth registration district, date of birth (same year), father's occupational group                                                                                                         | Women: p=0.20<br>Men: OR 1.13 95%CI 1.06-1.20<br>Both in a model with paternal age, for women effect was significant when testing maternal age separately                                    | -                                                                                                             |                                                                                                                                                                                                                                                  |
|                       |    | Paternal age               | Included in adjusted model: parental and maternal age in one model                                                                                                                                                                            | Women: p=0.19<br>Men: OR 1.13 95%CI 1.06-1.20 p<0.001<br>Both in a model with maternal age, for women effect was significant when testing maternal age separately                            |                                                                                                               |                                                                                                                                                                                                                                                  |
| <i>Cohort studies</i> |    |                            |                                                                                                                                                                                                                                               |                                                                                                                                                                                              |                                                                                                               |                                                                                                                                                                                                                                                  |
| Lahti                 | 67 | Maternal grand multiparity | Cox proportional hazards models, sex specific results<br><br>Model 1: Adjusted for year of birth (1934-1938 or 1939-1944), mother's and father's highest attained occupational statuses, birth weight, maternal body mass index at childbirth | Women<br>Model 1 HR 0.73 95%CI 0.10-5.40, p=0.76<br>Model 2 HR 0.79 95%CI 0.10-6.05, p=0.82<br><br>Men<br>Model 1 HR 1.07 95%CI 0.25-4.45, p=0.93<br>Model 2 HR 1.32 95%CI 0.31-5.62, p=0.70 | -                                                                                                             | -                                                                                                                                                                                                                                                |

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Model 2: Adjusted for year of birth  
(1934-1938 or 1939-1944), mother's  
and father's highest attained  
occupational statuses, birth weight,  
maternal body  
mass index at childbirth, and maternal  
age at childbirth.

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Subgroup results from studies regarding parental age and/or birth order.

AD=Alzheimer's disease



## Season of birth

| Author               | Ref. | Exposure                     | Sex-specific analysis                                                                                                                                           | Other sub-group analyses                                                                                                                                                                                                                              |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------|------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      |      |                              | Description and statistical test                                                                                                                                | Results (by exposure)                                                                                                                                                                                                                                 | Description and statistical test                                                                                                                                                           | Results (by exposure)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Season of birth      |      |                              |                                                                                                                                                                 |                                                                                                                                                                                                                                                       |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Case-control studies |      |                              |                                                                                                                                                                 |                                                                                                                                                                                                                                                       |                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Dysken               | 68   | Season of birth (by quarter) | Chi-squared analysis: observed vs expected births, individual quarter vs remaining quarters (yates correction); Edwards' procedure for estimating cyclic trends | No sex effects where observed in the chi-squared analyses.<br><br>Edwards' test for peak quarter was significant for women ( $\chi^2=7.0$ , $df=2$ , $p<0.05$ ), peak period occurring early in the first quarter; no peak was established for AD men | Chi-squared analysis: observed vs expected births, individual quarter vs remaining quarters (yates correction); family history of AD                                                       | Family history chi-squared: 1.14 (NS)<br>No family history chi-squared: 1.93 (NS)<br>Individual quarter vs remaining quarters: NS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Henderson            | 69   | Season of birth (by quarter) | -                                                                                                                                                               | -                                                                                                                                                                                                                                                     | Chi-squared test and Roger's methods for cyclic trends<br><br>Family history of dementia<br><br>Early (<75 years) or late-onset cases ( $\geq 75$ years)<br><br>Southern hemisphere births | Per quarter 'Familial' cases<br>Cases vs controls: chi-squared: 4.22 $p=0.24$<br>Cases vs general population: chi-squared: 6.88 $p=0.08$<br>Roger's test: chi-square: 4.46 $p=0.11$<br><br>'Sporadic' cases<br>Cases vs controls: chi-squared: 1.91 $p=0.59$<br>Cases vs general population: chi-squared: 0.95 $p=0.81$<br>Roger's test: chi-square: 1.34 $p=0.51$<br><br>Early-onset cases (<75 years)<br>Cases vs controls: chi-squared: 2.54 $p=0.67$<br>Cases vs general population: chi-squared: 2.72 $p=0.44$<br>Roger's test: chi-squared: 1.95 $p=0.38$<br><br>Early-onset cases (<75 years)<br>Cases vs controls: chi-squared: 0.95 $p=0.81$<br>Cases vs general population: chi-squared: 2.86 $p=0.41$<br>Roger's test: chi-squared: 0.30 $p=0.86$<br><br>All aforementioned results were additionally shown for Southern hemisphere births only; Results were not statistically significant expect for |

|           |    |                                         |   |   |                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------|----|-----------------------------------------|---|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           |    |                                         |   |   |                                                                                                                                                                                                                               | the Roger's test in 'familial' cases: 5.91 p=0.05; proportionally fewer births in the southern summer months of January and February                                                                                                                                                                                                                                                                                                                                                                                                               |
| Philpot   | 73 | Season of birth (per quarter)           | - | - | Chi-squared test for observed vs expected births and Roger's method for testing cyclic trends and Edwards' method for determining the peak quarter of birth<br><br>With and without a family history of dementia for AD cases | With and without family history for AD patients<br>Family history: Chi-squared (df=3): 3.04 p>0.1<br>Without a family history: Chi-squared: 14.85 p<0.01<br><br>AD patients without family history of dementia, significance of cyclical trend (Roger's method) p<0.05; peak quarter (Edward's method) early 1st.<br><br>AD patients without family history of dementia, significance of cyclical trend p<0.4, peak quarter early 3rd<br><br>General population 1971 1% sample; cyclical trend P<0.0005; peak quarter May; as shown for comparison |
| Ptok 2001 | 70 | Season of birth (quarterly birth rates) | - | - | Chi-squared test; comorbid AD and depression; ApoE4 negative or positive for AD and comorbid AD and depression                                                                                                                | Comorbid AD and depression vs controls, chi-squared: 0.65 p=0.89<br>AD and co-morbid AD and depression - ApoE4 negative, chi-squared: 4.14 p=0.25<br>AD and co-morbid AD and depression - ApoE4 positive, chi-squared: 1.36 p=0.72                                                                                                                                                                                                                                                                                                                 |
| Vitiello  | 71 | Season of birth (quarterly birth rates) | - | - | Chi-squared test; Edwards method for cyclic trend                                                                                                                                                                             | Patients with AD with negative family history of AD compared to controls.<br>Chi-squared: 4.0 (df=3) p=0.26                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Ding      | 78 | Season of birth                         | - | - | Logistic regression; residence (urban or rural), geographic region (north or south); adjusted for: age, gender, education and annual household income per capita                                                              | Urban residence:<br>Spring (Mar, Apr, May) OR 0.64 95%CI 0.49-0.84 p=0.002<br>Summer Reference<br>Autumn (Sep, Oct, Nov) OR 0.80 95%CI 0.62-1.03 p=0.084<br>Winter (Dec, Jan, Feb) OR 0.63 95%CI 0.49-0.83 p=0.001<br><br>Rural residence:<br>Spring (Mar, Apr, May) OR 0.98 95%CI 0.80-1.21 p=0.868<br>Summer Reference                                                                                                                                                                                                                           |

|  |  |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--|--|--|--|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  |  |  |  |  | <p>Autumn (Sep, Oct, Nov) OR 0.95 95%CI 0.77-1.17 p=0.644</p> <p>Winter (Dec, Jan, Feb) OR 0.84 95%CI 0.67-1.04 p=0.109</p> <p>North:</p> <p>Spring (Mar, Apr, May) OR 0.82 95%CI 0.64-1.05 p=0.117</p> <p>Summer Reference</p> <p>Autumn (Sep, Oct, Nov) OR 0.79 95%CI 0.62-1.01 p=0.063</p> <p>Winter (Dec, Jan, Feb) OR 0.66 95%CI 0.51-0.86 p=0.002</p> <p>South:</p> <p>Spring (Mar, Apr, May) OR 0.88 95%CI 0.70-1.10 p=0.259</p> <p>Summer Reference</p> <p>Autumn (Sep, Oct, Nov) OR 0.97 95%CI 0.78-1.20 p=0.753</p> <p>Winter (Dec, Jan, Feb) OR 0.83 95%CI 0.67-1.03 p=0.097</p> |
|--|--|--|--|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <i>Cohort studies</i> |    |                |                                    |                                                  |                                    |                                                                                                                                                                                                                                                      |
|-----------------------|----|----------------|------------------------------------|--------------------------------------------------|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hsu                   | 81 | Month of birth | Walter & Elwood's seasonality test | Performing the analysis in men alone<br>P <0.001 | Walter & Elwood's seasonality test | <p>Diagnosis occurred at least 3 times<br/>P &lt;0.001</p> <p>Comorbidities ≤ 1<br/>P &lt;0.001</p> <p>Younger onset (below average)<br/>P &lt;0.001</p> <p>Higher urbanization<br/>P &lt;0.001</p> <p>Income lower than average<br/>P &lt;0.001</p> |

Subgroup results from studies regarding season of birth.

AD=Alzheimer's disease

## Place of birth

| Author               | Ref. | Exposure                                                   | Sex-specific analysis                                                                                                                                                  |                       | Other sub-group analyses                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------|------|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      |      |                                                            | Description and statistical test                                                                                                                                       | Results (by exposure) | Description and statistical test                                                                                                            | Results (by exposure)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Place of birth       |      |                                                            |                                                                                                                                                                        |                       |                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Case-control studies |      |                                                            |                                                                                                                                                                        |                       |                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Forster              | 48   | Place of birth (Aluminium concentration in drinking water) | -                                                                                                                                                                      | -                     | OR's calculated with McNemar's test (taking matching into account)<br><br>With and without a familial case of AD                            | No differences compared to overall results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Glymour              | 86   | Place of birth (Stroke belt vs outside stroke belt)        | -                                                                                                                                                                      | -                     | Mortality rates; logistic regression<br>Crude model: adjusted for age, age-squared and sex<br><br>Stratified by adult stroke belt residence | Adult stroke belt residence (2000)<br>White<br>All cause dementia OR 1.22 95%CI 1.20-1.25<br>Alzheimer's disease OR 1.33 95%CI 1.27-1.35<br><br>African American<br>All cause dementia OR 1.21 95%CI 1.15-1.26<br>Alzheimer's disease OR 1.27 95%CI 1.17-1.37<br><br>No adult stroke belt residence (2000)<br>White<br>All cause dementia OR 1.25 95%CI 1.22-1.29<br>Alzheimer's disease OR 1.30 95%CI 1.24-1.36<br><br>African American<br>All cause dementia OR 1.29 95%CI 1.24-1.36<br>Alzheimer's disease OR 1.27 95%CI 1.17-1.37 |
| Jean                 | 82   | Place of birth (rural and urban vs reference population)   | Rural<br>Men OR=0.83<br>Women OR=1.79*<br><br>Urban<br>Men OR=0.38*<br>Women OR=1.33*<br><br>Total<br>Men OR=0.54*<br>Women OR=1.49*<br><br>*statistically significant | -                     | Analysis were repeated without kin pairs at a three generation depth                                                                        | Rural<br>Men OR=0.67*<br>Women OR=1.81*<br><br>Urban<br>Men OR=0.39*<br>Women OR=1.41*<br><br>Total<br>Men OR=0.48*<br>Women OR=1.55*<br><br>*statistically significant                                                                                                                                                                                                                                                                                                                                                               |

| <i>Cohort studies</i>                                   |    |                                                       |   |   |                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                        |
|---------------------------------------------------------|----|-------------------------------------------------------|---|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gilsanz<br>2017                                         | 85 | Place of birth<br>(in high stroke<br>mortality state) | - | - | <p>Cox proportional hazard models with age as the time scale; cumulative risk of dementia</p> <p>Crude model: adjusted for age and sex<br/>Fully adjusted model: adjusted for age, sex, education, midlife (BMI, smoking duration, hypertension) and late life (diabetes, hypertension, heart failure, acute myocardial infarction and stroke) cardiovascular risk factors</p> | <p>Crude model:<br/>Black participants HR 1.13 95%CI 0.94-1.35<br/>Non-black participants HR 1.46 95%CI 1.23-1.74</p> <p>Fully adjusted model:<br/>Black participants HR 1.14 95% CI 0.95-1.36<br/>Non-black participants HR 1.42 95% CI 1.19-1.69</p> |
| Subgroup results from studies regarding place of birth. |    |                                                       |   |   |                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                        |
| AD=Alzheimer's disease                                  |    |                                                       |   |   |                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                        |

## Other factors

| Author         | Ref. | Exposure                                  | Sex-specific analysis                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Other sub-group analyses                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------|------|-------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                |      |                                           | Description and statistical test                                       | Results (by exposure)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Description and statistical test                                                                                                                                                                                                               | Results (by exposure)                                                                                                                                                                                                                                                                                                                                                                                                          |
| Other factors  |      |                                           |                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Cohort studies |      |                                           |                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Cocoros        | 93   | Prenatal 1918 influenza pandemic exposure | Poisson regression; incidence rate ratios (IRR); sex-specific analysis | Women:<br>All ages: 1.02 95%CI 0.99-1.05<br>62-72: 0.96 95%CI 0.86-1.07<br>72-82: 1.05 95%CI 1.00-1.11<br>82-92: 1.01 95%CI 0.97-1.04<br><br>AD 1.01 95%CI 0.96-1.06<br>Vascular dementia 1.04 95%CI 0.96-1.12<br>Other dementia 1.02 95%CI 0.98-1.06<br><br>Men:<br>All ages: 1.01 95%CI 0.97-1.05<br>62-72: 0.82 95%CI 0.74-0.92<br>72-82: 1.07 95%CI 1.01-1.13<br>82-92: 1.00 95%CI 0.95-1.06<br><br>AD 0.91 95%CI 0.85-0.97<br>Vascular dementia 1.04 95%CI 0.95-1.14<br>Other dementia 1.06 95%CI 1.01-1.11 | Poisson regression; incidence rate ratios (IRR); included in the model: sex.<br><br>Sensitivity analysis<br>-By age<br>-Inpatient only<br>-restricted to those exposed during the first trimester compared to those born before June 1918 only | By age:<br>62-72: IRR 0.89 95%CI 0.82-0.96<br>72-82: IRR 1.06 95%CI 1.02-1.10<br>>82: IRR 1.01 95%CI 0.98-1.04<br><br>Inpatient only<br>Generally similar results; some significant results, however, point estimates were modest<br><br>First trimester compared to born before June 1918; generally similar results; some significant results, however, point estimates were modest<br><br>Any dementia 1.02 95%CI 0.96-1.08 |
| Kang           | 94   | Prenatal famine exposure                  |                                                                        | There was no difference among men and women subgroups                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                |

Subgroup results from studies regarding other factors.

AD=Alzheimer's disease

## Birth characteristics

| Author                                                         | Ref. | Exposure                     | Sex-specific analysis                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                            | Other sub-group analyses                                                                                                                                                                             |                                                                            |
|----------------------------------------------------------------|------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
|                                                                |      |                              | Description and statistical test                                                                                                              | Results (by exposure)                                                                                                                                                                                                                                                                                                                                                                                                                      | Description and statistical test                                                                                                                                                                     | Results (by exposure)                                                      |
| Birth size                                                     |      |                              |                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                      |                                                                            |
| Cohort studies                                                 |      |                              |                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                      |                                                                            |
| Mosing                                                         | 66   | Birth weight (z-score)       |                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                            | Within-pair analyses in monozygotic twins and in monozygotic (MZ) twins and same-sex dizygotic (DZ) twin pairs; conditional cox regression models with family identification as the stratum variable | MZ twins: 0.81 95%CI 0.53-1.24<br>MZ and same-sex DZ: 0.90 95%CI 0.71-1.15 |
|                                                                |      | Head circumference (z-score) |                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                      | MZ twins: 0.83 95%CI 0.53-1.29<br>MZ and same-sex DZ: 0.92 95%CI 0.71-1.21 |
| Syddall                                                        | 100  | Birth weight                 | Cox proportional hazards model; hazard ratio presented per standard deviation increase in birth weight; birth year was included in the models | Men:<br>Dementia HR 1.63 95%CI 1.10-2.43 p=0.02 (13 deaths)<br>AD HR 0.60 95%CI 0.32-1.13 p=0.12 (8 deaths)<br><br>Women:<br>Dementia 0.66 (0.23-1.91) p=0.44 (3 deaths)<br>AD 3.29, 95%CI 1.67-6.48 p= 0.001 (5 deaths)<br>Results were consistent in an analysis of mortality by age 75 years and 65 years<br><br>Excluding women who weighed more than 4 kg at birth attenuated the associations of birth weight with mortality from AD | -                                                                                                                                                                                                    | -                                                                          |
| Subgroup results from studies regarding birth characteristics. |      |                              |                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                      |                                                                            |

AD=Alzheimer's disease