

# Supplementary Material

## Population Attributable Fractions for Modifiable Risk Factors of Incident Dementia in Cognitively Normal and Mild Cognitively Impaired Older Adults: Data from Two Cohort Studies

**Supplementary Table 1.** Definitions of risk factors

Risk factor	Definition of risk factors
Low education	B: Having had less than 12 years of education/less than 4 years high school
Hearing loss	N: Self-reported hearing impairment at baseline H: Observed normal or abnormal hearing
Hypertension	B: Self-reported diagnosis of hypertension at baseline or history of hypertension
Diabetes	B: Self-report of diagnosis of diabetes at baseline or history of diabetes
Obesity	B: BMI with weight and height measured by the NACC or HEIAD research team
Smoking	N: Self-reported having smoked more than 100 cigarettes during life H: self-reported current smoking
Depression	N: Diagnosis of depression at baseline (according to DSM 4 <sup>th</sup> edition) following a structured Geriatric Mental State interview and self-reported previous depression H: Diagnosis of depression (according to DSM 4 <sup>th</sup> edition) based on clinical impression of Neurologists
Physical inactivity	H: Self-report of physical exercise less than once per month or less than one hour a day in motion
Social isolation	H: Social contact occurring less than once per month, calculated using self-reported physical contact frequency with friends, relatives, or children
TBI	B: Self-report of history of TBI. TBI is defined as damage inflicted on brain tissues by a direct or indirect effect of an external force, with possible or no disruption of structural continuity [32].
Excessive alcohol use	N: Clinically significant impairment occurring over a 12-month period manifested in one of the following areas: work, driving, legal or social

H, HELIAD; N, NACC; B, both

**Supplementary Table 2.** Definitions of confounding factors

---

Confounding factor	Definition of factor
Age	B: Age at initial visit
Sex	B: Registered sex
Race	N: Caucasian, African, Asian, multiracial, other
<i>APOE</i>	B: Obtained genetic information about the number of $\epsilon 4$ alleles (0, 1, 2)
Sleep disorder	H: Self-reported incidence or history of rem sleep disorder, insomnia (trouble falling asleep or sleeping trough) or apnea.
Mediterranean diet	H: Total score of the Mediterranean Dietary Score (0-55). Information obtained via the food frequency questionnaire
Cognitive activity	H: Having visited a museum or read a book, newspaper or magazine at least once a month
Moderate alcohol use	H: Self-reported drinking of alcohol in the past

---

H, HELIAD; N, NACC; B, both

## Formula of the PAFs

PAF values are calculated as

$$PAF = \frac{P(HR - 1)}{1 + P(HR - 1)} ,$$

where  $P$  is the prevalence of the risk factor and  $HR$  the relative risk of incident dementia due to exposure to that risk factor. Estimates of risk factor prevalence were made on the prevalence of a risk factor in the datasets of this study.

The (weighted) overall PAF is the proportional reduction in prevalence of dementia in the population that would occur if exposure to this set of risk factors were reduced to an alternative ideal exposure scenario [33]. The overall PAF is given by

$$Overall\ PAF = 1 - [(1 - PAF_1^+)(1 - PAF_2^+) \dots],$$

where each  $PAF^+$  is in the set of strictly positive PAF values.

Weighted PAF is the relative contribution of each risk factor to the overall PAF. Each individual risk factor's PAF was weighted via

$$Weighted\ PAF = \frac{PAF}{\sum PAF} \cdot Overall\ PAF,$$

where  $\sum PAF$  is the sum of all individual PAFs.

The overall weighted PAF is calculated based on the weighted PAF for each individual risk factor using the formula:

$$Overall\ Weighted\ PAF = 1 - [(1 - Weighted\ PAF_1)(1 - Weighted\ PAF_2) \dots].$$

**Supplementary Table 3.** These results of crosstabs show the percentage of risk factor prevalence for the complete and missing data of the NACC data after imputation

NACC imputation	Missing data	Complete data	Total
Sex, female	60.1%	58.6%	59.0%
Low education, yes	6.7%	4.9%	5.3%
Hypertension, yes	61.4%	56.5%	57.7%
Diabetes, yes	15.1%	13.1%	13.5%
Obesity, yes	26.4%	23.4%	24.0%
Hearing loss, yes	25.4%	25.0%	25.1%
TBI, yes	10.3%	11.2%	11.0%
Excessive alcohol use, yes	4.4%	3.9%	4.0%
Depression, yes	30.0%	28.4%	28.7%
Smoking, yes	46.2%	47.5%	47.2%

**Supplementary Table 4.** These results of crosstabs show the percentage of risk factor prevalence for the complete and missing data of risk factors of the HELIAD data after imputation

HELIAD imputation	Missing data	Complete data	Total
Sex, female	59.5%	57.9%	58.0%
Low education, yes	38.9%	32.5%	32.9%
Hypertension, yes	70.7%	64.5%	65.0%
Diabetes, yes	20.0%	16.7%	17.0%
Obesity, yes	36.8%	36.0%	36.1%
Hearing loss, yes	11.9%	9.3%	9.5%
TBI, yes	5.5%	11.9%	11.4%
Depression, yes	12.1%	12.3%	12.3%
Smoking, yes	45.1%	39.0%	39.5%
Social isolation, yes	27.4%	40.4%	39.2%
Physical inactivity, yes	82.9%	84.6%	84.4%

**Supplementary Table 5.** HRs for dementia risk of the total sample, CN subgroup and MCI subgroup of the NACC data before imputation

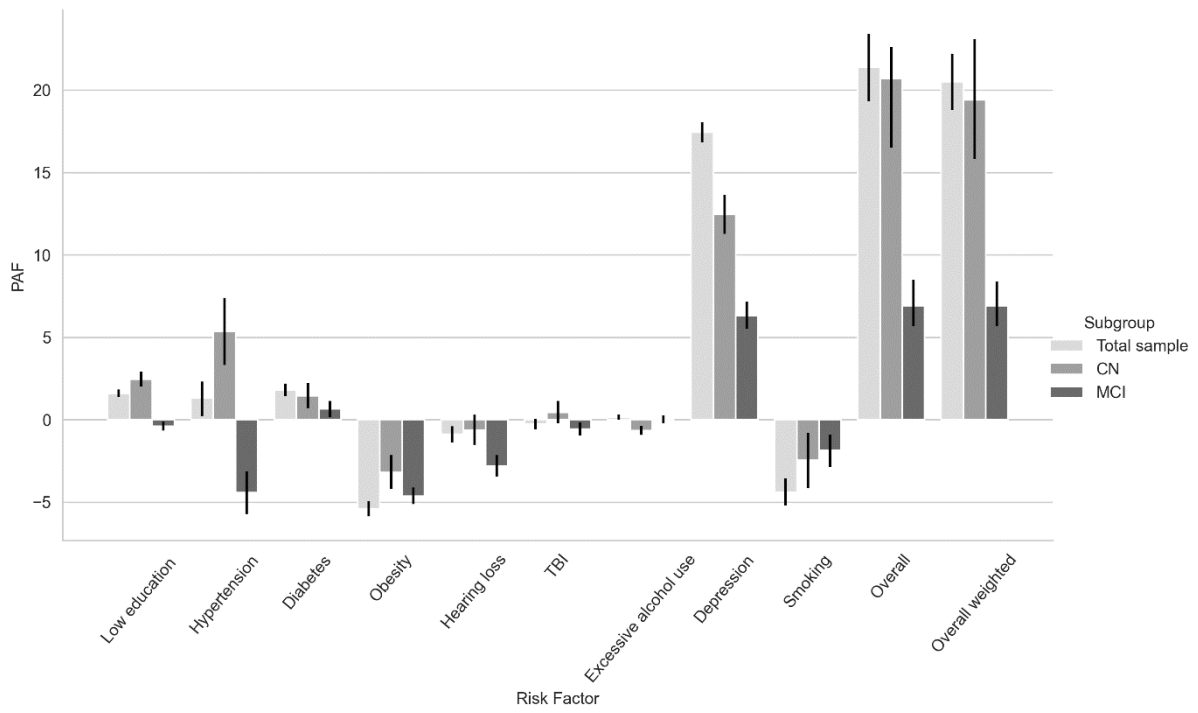
NACC (unimputed)	HR total sample (95% CI)	HR CN (95% CI)	HR MCI (95% CI)
Low education	1.32 (1.12–1.55)**	1.62 (1.17–2.24)**	0.94 (0.77–1.15)
Hypertension	1.05 (0.97–1.13)	1.08 (0.93–1.26)	0.94 (0.85–1.02)
Diabetes	1.19 (1.06–1.32)**	1.12 (0.88–1.41)	1.02 (0.90–1.16)
Obesity	0.81 (0.73–0.90)***	0.90 (0.73–1.09)	0.77 (0.68–0.87)***
Hearing loss	0.99 (0.91–1.08)	0.95 (0.80–1.13)	0.93 (0.84–1.03)
TBI	1.01 (0.89–1.14)	1.04 (0.80–1.34)	0.94 (0.84–1.09)
Excessive alcohol use	1.20 (1.00–1.43)	1.01 (0.66–1.57)	1.03 (0.84–1.26)
Depression	1.57 (1.45–1.70)***	1.42 (1.20–1.68)***	1.08 (0.98–1.19)
Smoking	0.91 (0.85–0.98)*	0.93 (0.80–1.08)	0.93 (0.85–1.02)

HR, hazard ratio; CI, confidence interval; CN, cognitively normal; MCI, mild cognitive impairment; TBI, traumatic brain injury

Multivariable models adjusted for age, sex, race, and *APOE*  $\epsilon 4$ .

\* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$

**Supplementary Figure 1.** PAFs of dementia for the total sample, CN, and MCI subgroup of the NACC.



PAF, population attributable fraction; CN, cognitively normal; MCI, mild cognitive impairment

**Supplementary Table 6.** PAFs for dementia risk for the total sample, CN subgroup and MCI subgroup of the NACC data before imputation

NACC (unimputed)	PAF total sample (95% CI)	PAF CN (95% CI)	PAF MCI (95% CI)
Low education	1.68 (0.66–2.86)	2.54 (0.72–4.94)	-0.40 (-1.56–0.98)
Hypertension	2.70 (-1.64–6.99)	4.52 (-3.87–12.71)	-3.98 (-9.46–1.42)
Diabetes	2.44 (0.82–4.19)	1.40 (-1.46–4.79)	0.34 (-1.63–2.49)
Obesity	-4.79 (-6.91–-2.54)	-2.69 (-7.19–2.31)	-5.31 (-7.56–-2.88)
Hearing loss	-0.16 (-2.24–2.02)	-1.10 (-4.79–2.97)	-2.07 (-4.81–0.80)
TBI	0.08 (-1.20–1.48)	0.36 (-2.11–3.39)	-0.70 (-2.22–1.01)
Excessive alcohol use	0.78 (0.01–1.69)	0.04 (-1.08–1.73)	0.14 (-0.84–1.31)
Depression	14.09 (11.47–16.76)	8.97 (4.46–13.79)	2.84 (-0.60–6.36)
Smoking	-4.34 (-7.80–-0.86)	-3.48 (-10.29–3.43)	-3.23 (-7.37–0.95)
Overall*	20.51 (12.78–31.62)	16.82 (5.15–40.82)	3.30 (0–14.44)
Overall weighted*	19.39 (12.61–28.22)	15.91 (5.12–34.54)	3.29 (0–13.66)

PAF, population attributable fraction, CI, confidence interval; CN, cognitively normal; MCI, mild cognitive impairment; TBI, traumatic brain injury

\*Negative PAFs were omitted in the calculation of the overall PAF.



**Supplementary Table 7.** HRs for dementia risk in the total sample, CN subgroup and MCI subgroup of the HELIAD data before imputation

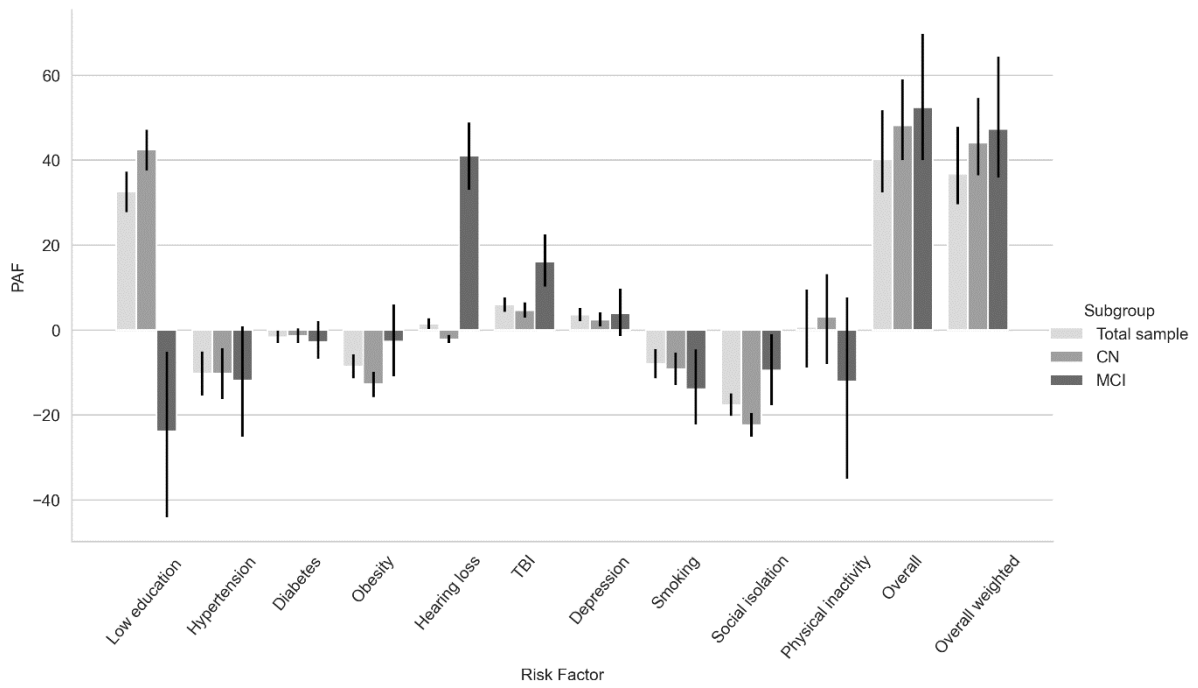
HELIAD (unimputed)	HR total sample (95% CI)	HR CN (95% CI)	HR MCI (95% CI)
Low education	1.42 (0.73–2.76)	1.91 (0.82–4.45)	0.97 (0.37–2.58)
Hypertension	0.83 (0.49–1.41)	0.62 (0.30–1.28)	0.99 (0.99–1.00)***
Diabetes	0.99 (0.99–1.00)**	0.75 (0.32–1.77)	0.99 (0.99–1.00)***
Obesity	1.06 (0.61–1.85)	1.86 (0.91–3.77)	0.61 (0.24–1.51)
Hearing loss	0.98 (0.56–1.70)	0.34 (0.07–1.59)	1.11 (0.81–1.52)
TBI	0.99 (0.99–1.00)***	0.99 (0.99–1.00)***	0.99 (0.99–1.00)**
Depression	1.00 (0.99–1.00)	1.00 (0.99–1.00)	0.50 (0.18–1.36)
Smoking	0.90 (0.46–1.76)	1.29 (0.57–2.94)	0.35 (0.12–1.00)**
Social isolation	1.04 (0.61–1.78)	1.71 (0.79–3.71)	0.39 (0.16–0.94)**
Physical inactive	3.62 (0.85–1.55)	4.20 (0.53–3.34)	3.86 (0.60–2.50)

HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment; TBI, traumatic brain injury

Multivariable models adjusted for age, sex, alcohol use, sleep disorder, cog activity, and diet.

\* $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\* $p \leq 0.001$

**Supplementary Figure 2.** PAFs of dementia for the total sample, CN, and MCI subgroup of the HELIAD



PAF, population attributable fraction; CN, cognitively normal; MCI, mild cognitive impairment

**Supplementary Table 8.** PAFs for dementia risk for the total sample, CN subgroup and MCI subgroup of the HELIAD data before imputation

HELIAD (unimputed)	PAF total sample (95% CI)	PAF CN (95% CI)	PAF MCI (95% CI)
Low education	21.84 (-22.56–54.22)	37.66 (-13.28–69.52)	-1.91 (-89.81–54.16)
Hypertension	-12.45 (-49.86–21.04)	-33.03 (-83.99–15.46)	-0.40 (-0.56–-0.24)
Diabetes	-0.12 (-0.20–-0.04)	-4.34 (-12.90–11.44)	-0.10 (-0.14–-0.07)
Obesity	2.26 (-16.28–23.47)	23.47 (-3.17–49.81)	-17.85 (-41.22–16.57)
Hearing loss	-0.24 (-4.38–6.25)	-5.78 (-8.33–4.63)	2.15 (-3.85–9.31)
TBI	-0.07 (-0.09–-0.05)	-0.07 (-0.10–-0.04)	-0.11 (-0.18–-0.04)
Depression	-0.04 (-0.14–0.05)	-0.02 (-0.07–0.03)	-13.87 (-24.85–8.07)
Smoking	-4.15 (-27.11–23.04)	10.25 (-20.60–43.27)	-35.13 (-54.07–-0.04)
Social isolation	1.66 (-18.07–23.53)	21.44 (-9.00–51.10)	-37.05 (-59.14–-2.80)
Physical inactivity	68.90 (-14.84–31.75)	72.96 (-66.54–66.43)	71.05 (-53.13–56.30)
Overall*	76.64 (0–89.59)	90.9 (0–98.98)	71.67 (0–86.07)
Overall weighted*	64.74 (0–62.45)	65.46 (0–66.23)	70.20 (0–63.54)

PAF, population attributable fractions; CI, confidence interval; MCI, mild cognitive impairment; TBI, traumatic brain injury

\*Negative PAFs were omitted in the calculation of the overall PAF.

**Supplementary Table 9.** Logistic regression of dementia of the total sample of the NACC

	B (CI 95%)
Low education	0.31 (0.19–0.43)***
Hypertension	0.04 (-0.05–0.14)
Diabetes	0.17 (0.04–0.31)**
Obesity	-0.32 (-0.44–-0.20)***
Hearing loss	-0.01 (-0.12–0.10)
TBI	-0.09(-0.23–0.06)
Excessive alcohol use	-0.09 (-0.32–0.15)
Depression	0.50 (0.40–0.60)***
Smoking	-0.07 (-0.16–0.030)

CI, confidence interval; TBI, traumatic brain injury  
Multivariable adjusted for age, sex, race, and *APOE* ε4.  
Weighting for education-sex is performed.

\* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$

**Supplementary Table 10.** Competing risk analyses of dementia of the total sample of the HELIAD with and without sleep and cognitive activity

HELIAD	HR total sample without sleep and cognitive activity (95% CI)	HR total sample with sleep and cognitive activity (95% CI)
Low education	1.79 (0.98–3.27)	1.58 (0.82–3.06)
Hypertension	0.94 (0.54–1.61)	0.91 (0.53–1.57)
Diabetes	1.19 (0.65–2.19)	1.09 (0.58–2.05)
Obesity	1.28 (0.75–2.17)	1.17 (0.68–2.01)
Hearing loss	1.07 (0.49–2.33)	1.09 (0.51–2.33)
TBI	1.72 (0.77–3.84)	1.64 (0.71–3.76)
Depression	1.54 (0.80–2.97)	1.49 (0.77–2.88)
Smoking	0.90 (0.48–1.69)	0.94 (0.50–1.76)
Social isolation	1.01 (0.60–1.72)	1.01 (0.60–1.70)
Physical inactive	4.39 (1.04–18.57)*	4.17 (0.98–17.84)*

HR, hazard ratio; CI, confidence interval; TBI, traumatic brain injury

Multivariable models adjusted for age, sex, alcohol use, and diet.

\* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$

**Supplementary Table 11.** Competing risk analyses of dementia of the total sample of the NACC with and without exclusion of participants that developed dementia within two years

NACC	HR total sample with exclusion of participants (95% CI)	HR total sample without exclusion of participants (95% CI)
Low education	1.51 (1.27–1.79)***	1.32 (1.12–1.55)**
Hypertension	1.01 (0.92–1.10)	1.05 (0.97–1.13)
Diabetes	1.15 (1.01–1.31)*	1.19 (1.06–1.32)**
Obesity	0.80 (0.72–0.90)***	0.81 (0.73–0.90)***
Hearing loss	0.93 (0.83–1.03)	0.99 (0.91–1.08)
TBI	1.13 (0.98–1.30)	1.01 (0.89–1.14)
Excessive alcohol use	1.17 (0.94–1.44)	1.20 (1.00–1.43)*
Depression	1.65 (1.51–1.81)***	1.57 (1.45–1.70)***
Smoking	0.91 (0.83–0.99)*	0.91 (0.85–0.98)*

HR, hazard ratio; CI, confidence interval; TBI, traumatic brain injury

Multivariable models adjusted for age, sex, *APOE* ε4, and race.

\* $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\* $p \leq 0.001$