Received: 15 June 2020 | Revised: 5 September 2020 | Accepted: 16 September 2020 | Published online: 13 October 2020

DOI: 10.1002/dad2.12116

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Multi-time-point data preparation robustly reveals MCI and dementia risk factors

Daman Kaur[1] | **Magda Bucholc**[2] | **David P. Finn**[3] | **Stephen Todd**[4] | **KongFatt Wong-Lin**[2] | **Paula L. McClean**[1]

[1] Northern Ireland Centre for Stratified Medicine, Biomedical Sciences Research Institute, Clinical Translational Research and Innovation Centre (C-TRIC), Altnagelvin Hospital Site, Ulster University, Derry/Londonderry, Northern Ireland, UK

[2] Intelligent Systems Research Centre, School of Computing, Engineering and Intelligent Systems, Ulster University, Derry/Londonderry, Northern Ireland, UK

[3] Pharmacology and Therapeutics, School of Medicine, Galway Neuroscience Centre, National University of Ireland Galway, University Road, Galway, Republic of Ireland

[4] Altnagelvin Area Hospital, Western Health and Social Care Trust, Derry/Londonderry, Northern Ireland, UK

Correspondence
Daman Kaur, Northern Ireland Centre for Stratified Medicine, Biomedical Sciences Research Institute, Ulster University, C-TRIC, Altnagelvin Hospital Site, Derry~Londonderry BT47 6SB, Northern Ireland, UK.
E-mail: kaur-d1@ulster.ac.uk

Abstract

Introduction: Conflicting results on dementia risk factors have been reported across studies. We hypothesize that variation in data preparation methods may partially contribute to this issue.

Methods: We propose a comprehensive data preparation approach comparing individuals with stable diagnosis over time to those who progress to mild cognitive impairment (MCI)/dementia. This was compared to the often-used "baseline" analysis. Multivariate logistic regression was used to evaluate both methods.

Results: The results obtained from sensitivity analyses were consistent with those from our multi-time-point data preparation approach, exhibiting its robustness. Compared to analysis using only baseline data, the number of significant risk factors identified in progression analyses was substantially lower. Additionally, we found that moderate depression increased healthy-to-MCI/dementia risk, while hypertension reduced MCI-to-dementia risk.

Discussion: Overall, multi-time-point–based data preparation approaches may pave the way for a better understanding of dementia risk factors, and address some of the reproducibility issues in the field.

KEYWORDS
baseline, cardiometabolic risk factors, dementia progression, longitudinal data, mild cognitive impairment (MCI), multi-time-point data preparation, multivariate logistic regression, National Alzheimer's Coordinating Center data

1 | BACKGROUND

Identifying risk factors for dementia is important not only for understanding its underlying pathologies, but also for suggesting potential interventions.[1] In particular, cardiometabolic risk factors have been suggested to play a significant role in dementia.[1–3] However, there remain considerable gaps in knowledge, given that several studies have reported contradictory results regarding the impact of such risk factors on cognitive decline and dementia.[2] For instance, a study by Solomon et al. analyzing midlife cholesterol levels in an American cohort (n = 9844), at baseline (ie, single time point), found an increased risk of dementia associated with elevated cholesterol.[4] However, another study analyzing a Swedish cohort (n = 1462) found no association between midlife cholesterol and dementia risk.[5] Similarly, another

study on data from the University of Alabama at Birmingham (UAB) Study of Aging,[6] analyzing baseline data on 624 individuals showed significant association between diabetes with cognitive decline, whereas a longitudinal study using the National Alzheimer's Coordinating Center (NACC) dataset (n = 11,777) observed no association between diabetes and cognitive decline.[7] In the case of hypertension, a study on the Neurological Disorders of Central Spain (NEDICES) cohort (n = 3824) showed increased risk of dementia with untreated baseline hypertension.[8] In contrast, the 90+ Study (n = 559) found lower dementia risk associated with baseline hypertension.[9] Both studies applied the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria to determine dementia diagnosis.

Closely related to cardiometabolic risk factors is midlife obesity, which has been reported to increase dementia risk.[1–3] However, this has been challenged by the UK CPRD (Clinical Practice Research Datalink) cohort (n = 1,958,191) findings, which revealed reduced dementia risk associated with midlife obesity.[10] Furthermore, considerable differences have been observed across studies on lifestyle-related risk factors, such as alcohol consumption and cigarette smoking, and their relationship with dementia risk.[11–14] Drinking and smoking patterns are differently recorded, for instance smoking in some studies is categorized as former, current, or never, whereas other studies measure cigarette pack-years.[13,14] With regard to the role of depression as a risk factor or a prodrome for cognitive impairment, it is still disputable.[15–17] The fact that the pathophysiological processes that lead to dementia occur decades before an official diagnosis is made further complicates our understanding of the dementia–depression relationship. Similarly, the association between depression and mild cognitive impairment (MCI), and the accompanying acceleration in progression to dementia, is evident in research; however, the cause-and-effect aspect remains debatable.[18,19]

Based on the plethora of conflicting findings relating to risk reported in the dementia field, it is clear we have a significant reproducibility crisis, and ambiguity regarding the nature of association between various risk factors and outcomes needs to be addressed. There can be several potential explanations; however, a key issue is that methodologies used to calculate risk are not consistently applied across studies. For example, there are differences in sample sizes,[4–9] inconsistent use of covariate/outcome definitions,[11–14] and differences in consideration of treated/untreated groups[8,9] and diagnostic criteria used.[4–7]

More importantly, for many risk factors, underlying pathologies and disease status vary over time, hence baseline values are not necessarily reflective of measurements at follow-ups.[20] Indeed, many individuals who are disease-free at baseline, subsequently acquire various medical conditions, including MCI and dementia as well as cardiovascular disease and stroke. Analysis on baseline values alone may therefore lead to misleading results.[20] Despite this, most studies do not account for temporal changes in risk factors.[4,6–9,20] Specifically, they underestimate the real strength of associations between risk factors and disease progression by relating the baseline value of a risk factor to outcome, even though it may substantially differ from the follow-up values (eg, changing body mass index [BMI]).

HIGHLIGHTS

- There are contradictory dementia risk analyses due to data preparation methods.
- Multi-time-point (MPT) versus baseline data was analyzed using logistic regression.
- The MPT approach reveals fewer mild cognitive impairment/dementia risk factors than baseline analyses.
- Sensitivity analyses show robust results based on the MPT approach.
- Depression enhances and hypertension reduces risk of progression to dementia.

RESEARCH IN CONTEXT

1. Systematic Review: Longitudinal dementia data were requested from the National Alzheimer's Coordinating Center (NACC) database. Additionally, we performed a literature survey using PubMed and Google Scholar to find relevant publications. Systematic review of risk factors in dementia highlighted significant ambiguity regarding the direction of risk associated with risk factors in dementia generally, and significant variability in data processing methods. There was no consensus or clarity on which attributes for a particular variable should be considered.
2. Interpretation: Using longitudinal NACC data we compare baseline analyses to a multi-time-point data preparation pipeline that we believe is more suitable for progression analyses. We demonstrate significant differences in the number of risk factors identified between baseline and progression analyses, suggestive of significant vulnerability to data processing methods.
3. Future Direction: Clear and unambiguous reporting of data preparation methods, particularly focusing on progression from healthy to mild cognitive impairment and dementia states may address reproducibility issues with respect to risk in dementia, and other diseases.

Several studies have previously adapted a multi-time-point analysis approach and developed predictive models for progression to dementia.[21–23] However, these studies analyzed risk factors that are numerical in nature such as cognitive test scores, hippocampal volume, total active voxels, etc.[21–23] Categorical risk factors, such as presence/absence of comorbidities, are not generally analyzed at multiple time points.

In the present study, we analyze several cardiometabolic comorbidities of dementia and other related risk factors using a comprehensive,

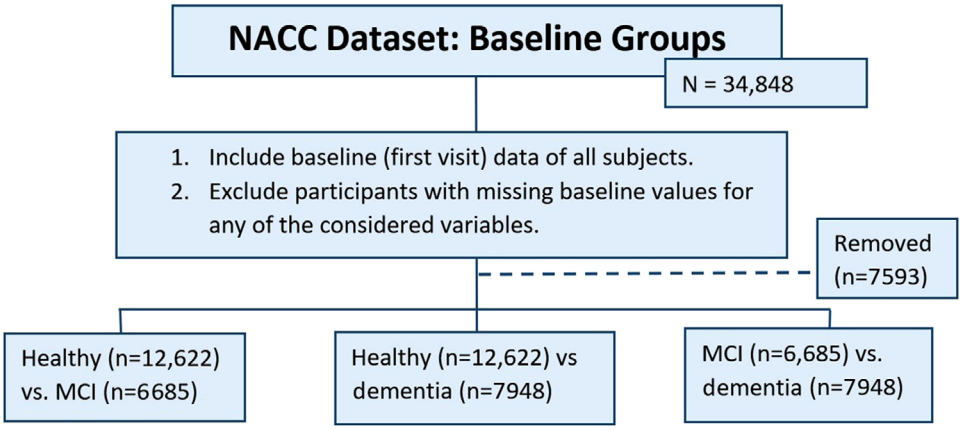


FIGURE 1 Data preparation process for baseline groups

multi-time-point data preparation approach. In this approach, data collated from several visits per individual is used to determine risk factors for healthy-to-MCI, healthy-to-dementia, and MCI-to-dementia conversion. Thereafter, given the measurements of risk factors from successive patient visits, we create a consistent set of rules for defining longitudinal changes, and accordingly estimate the effect of a set of potential risk factors on progression of disease severity. Subsequently, this was compared to the single-time-point analysis method. We believe that our multi-time-point approach better represents risk factor changes over time and helps minimize bias introduced by varying data preparation methods.

2 | METHODS

2.1 | Data source

The NACC dataset, one of the largest and most comprehensive longitudinal databases for dementia research, collated across the United States, was used in this study. It consists of more than 500 variables on lifestyle, genetic, and clinical data from more than 34,000 individuals.

Details about the NACC consortium and design and implementation of the NACC database have been described previously.[24]

The dataset used in our longitudinal investigation was the NACC Uniform Data Set (UDS; n = 34,848), collected from UDS visits conducted between September 2005 and June 2018. Written and informed consent was obtained from all participants and co-participants for the UDS by the Alzheimer's Disease Centers (ADCs). Among the risk factors in the NACC data, we selected age at visit, sex, years smoked, alcohol dependence, stroke, cardiac arrest/heart attack, diabetes, hypertension, hypercholesterolemia, BMI, and Geriatric Depression Scale (GDS) score. These were selected based on evidence from previous studies regarding their role in cognitive impairment.[1–4,6,8–14,25] Depression and lifestyle factors such as smoking and alcohol dependence are known to be strongly associated with metabolic disorders,[15–19,26] hence were included in this study. Incidence of MCI and all-cause dementia was determined based on clinical diagnosis. Due to low numbers of participants in progression groups, all-cause dementia was analyzed instead of specific dementia subtypes.

2.2 | Data preparation

Two data preparation approaches were compared in this study: the traditional baseline approach in which data were collected from the first patient visit (Figure 1; Section 2.2.1), and a multi-time-point progression approach in which data from multiple visits were collated for each participant (Figure 2; Section 2.2.2). This was done to reduce bias associated with a single measurement of a given risk factor, and to identify change in cognitive status over time. Individuals included in the analyses were aged ≥40 years.

2.2.1 | Baseline analyses

Observations from the first visit were analyzed for baseline groups. Three comparisons were made: healthy (n = 12,622) versus MCI (n = 6685), healthy (n = 12,622) versus dementia (n = 7948), and MCI (n = 6685) versus dementia (n = 7948). BMI was categorized as underweight-1 (< 18.5 kg/m^2), normal-2 (18.5–24.99 kg/m^2), or overweight-3 (> 24.99 kg/m^2), and GDS scores were categorized as no depression-1 (< 5), mild depression-2 (5–9), and moderate depression-3 (> 9). Individuals with missing baseline values (n = 7593) were excluded from the analysis (Figure 1).

2.2.2 | Progression analyses

Three comparisons were assessed for progression analyses: remained healthy (n = 5431) versus healthy-to-MCI (n = 543), remained healthy (n = 5431) versus realthy-to-dementia (n = 400), and remained MCI (n = 1141) versus MCI-to-dementia (n = 809). Figure 2 depicts the data preparation process for the progression groups, and Figure 3 depicts

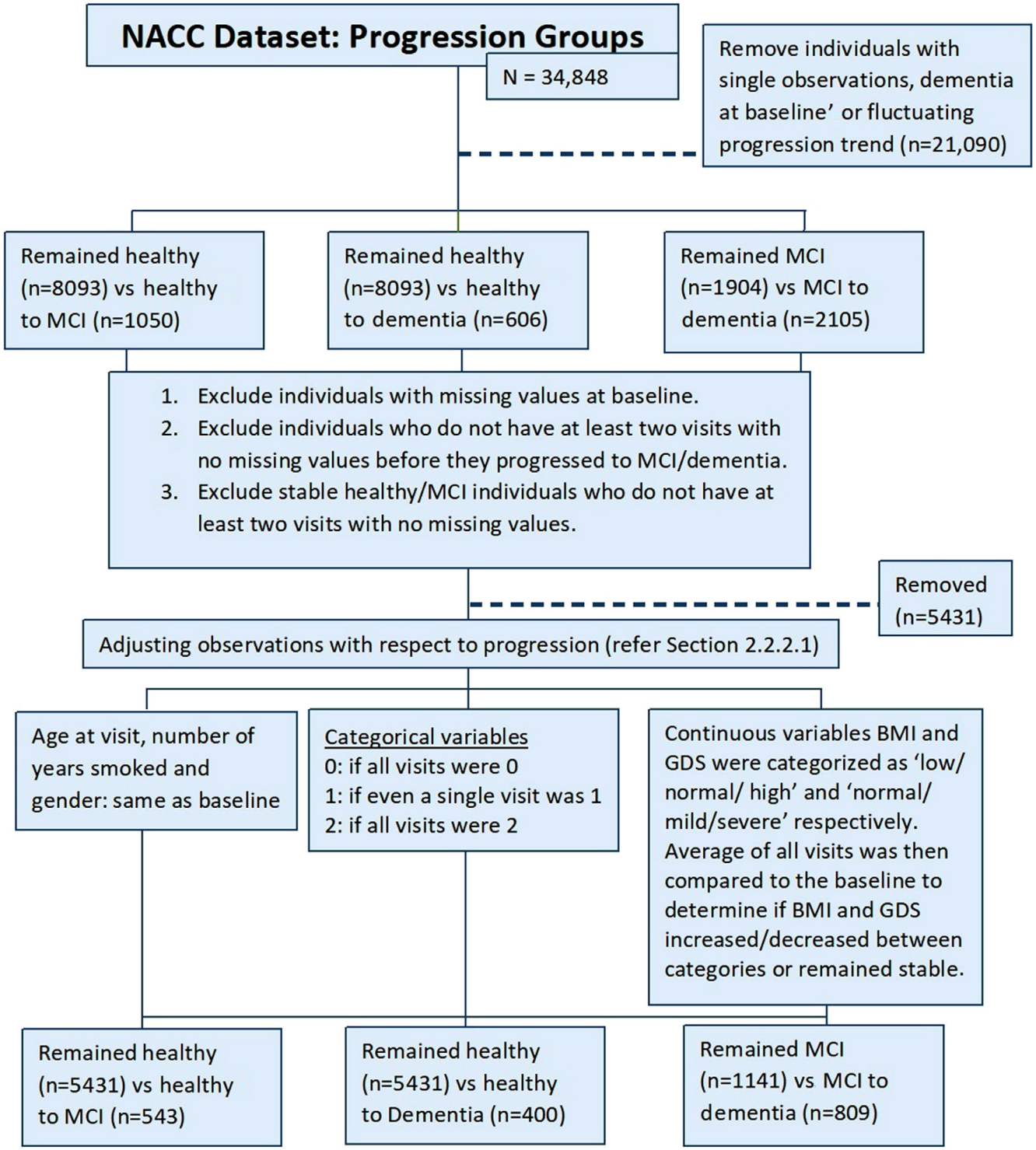


FIGURE 2 Data preparation process for progression groups within the NACC dataset. For categorical variables zero represents absent, one represents active/recent state (occurred within the last year or requiring active management) and two represents inactive/remote state (occurred in the past, more than 1 year ago but was resolved or there is no treatment currently under way). Abbreviations: BMI, body mass index; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Center

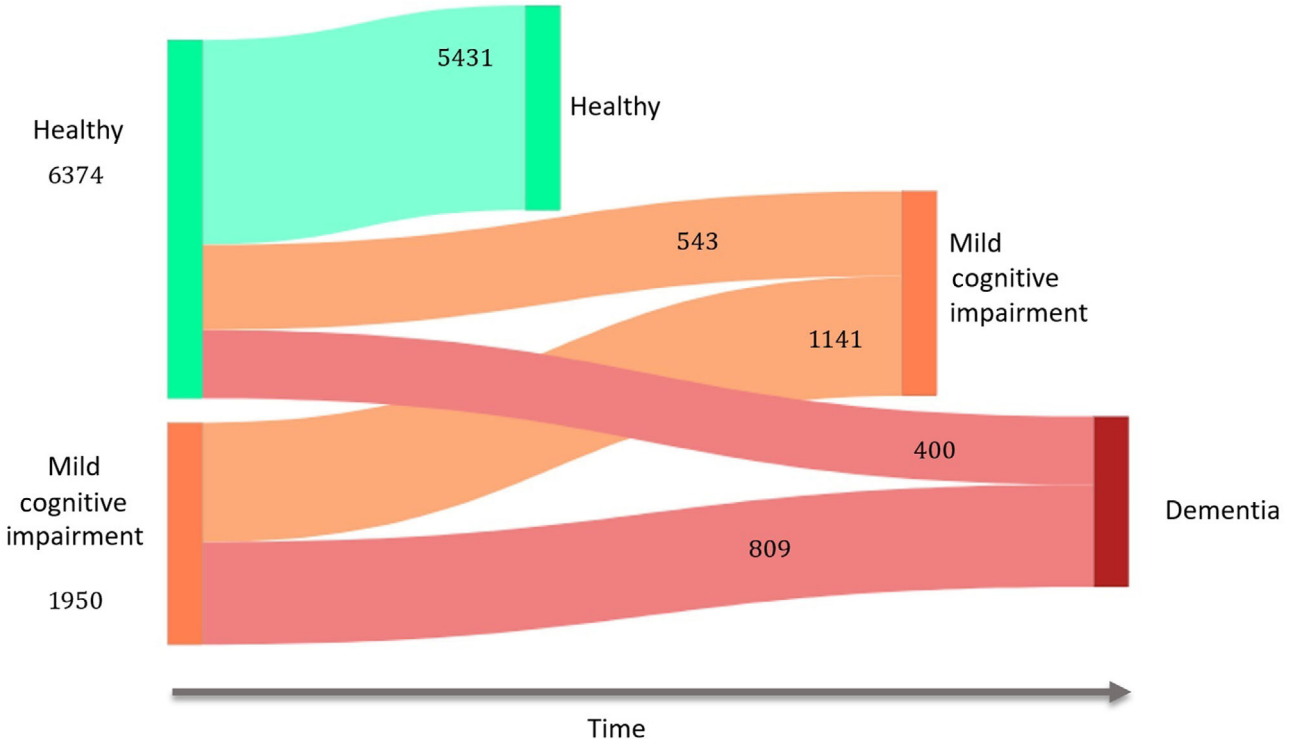


FIGURE 3 Transitions between different diagnostic groups over time in the National Alzheimer's Coordinating Center dataset

the transitions between diagnostic groups over time. The length of time from the first visit to subsequent diagnosis varied among the progression groups, ranging between 3.10 and 7.00 years (Table S1 in supporting information). Individuals with single observations, dementia at baseline, and those with alternating diagnosis between visits were excluded (n = 21,090). Moreover, those with missing values at baseline (n = 560) or only having complete observations for a single visit (n = 4871) were also excluded (Figure 2). Next, a multi-time-point approach was used to determine the status of risk factors given the data from multiple visits as explained in Section 2.2.2.1.

Adjusting observations with respect to progression

Numerous participants acquired conditions such as stroke, hypertension, and depression after their baseline visit. Accordingly, these variables are categorized differently at baseline and in subsequent visits. To account for this, we adjusted the values of independent variables to reflect how a particular risk factor developed beyond baseline. Instances in which a risk factor developed after the individual progressed to MCI/dementia were not considered.

Observations for age at visit, number of years smoked, and sex were obtained from baseline. Diabetes, hypertension, hypercholesterolemia, alcohol dependence, stroke, and heart attack/cardiac arrest are categorized in the NACC data as absent-0, active/recent-1 (occurred within the last year or requiring active management), or inactive/remote-2 (occurred in the past, ie, more than 1 year ago but was resolved or there is no treatment currently under way). For these variables, values were set to 0 if all visits were 0, 1 if a single visit was 1, and as 2 if all visits were 2.

BMI was first categorized as underweight-1 (< 18.5 kg/m^2), normal-2 (18.5–24.99 kg/m^2), or overweight-3 (> 24.99 kg/m^2). Change in BMI was determined by calculating the average of BMI categories (underweight, normal, or overweight) across all visits and qualitatively comparing this to the baseline category to determine increase/decrease/stable progression. Given that BMI can increase/decrease within the same category, we decided to take the average of BMI categories (as opposed to average of absolute BMI values) to represent transition between the groupings. Similarly, GDS scores were categorized as no depression-1 (< 5), mild depression-2 (5–9), and moderate depression-3 (> 9). Change in GDS was detected by calculating the average of GDS categories (none, mild, or moderate) across all visits and qualitatively comparing it to the baseline category to determine improvement/deterioration/maintenance of condition.

2.3 | Statistical analysis

Univariate analyses were performed to assess differences in demographic characteristics. The normality of data was assessed with Shapiro-Wilk test. The significance of differences between continuous variables was evaluated using an independent *t*-test for normally distributed data, and the Mann-Whitney U test for non-normally distributed data. To compare differences for categorical variables a chi-square test was applied. A multivariate logistic regression model was used to explore the relative contributions of the risk factors to MCI and all-cause dementia incidence at baseline, and for progression groups. False discovery rate (FDR) was applied to

adjust for multiple hypothesis testing by using the Benjamini-Yekutieli correction method.[27] FDR-adjusted *p*-values < 0.01 were considered statistically significant. Statistical analyses were performed using the "PredictABEL" package in R studio (Version 1.1.423).

2.3.1 | Sensitivity analysis

Sensitivity analyses were performed to assess the validity of our multi-time-point data preparation approach. We analyzed the baseline observations of non-converters versus baseline observations of converters from progression groups to assess any statistically significant differences between these groups. Hence, the following comparisons were analyzed: (1) baseline observations of individuals who remained healthy (n = 5431) versus baseline observations of healthy-to-MCI converters (n = 543); (2) baseline observations of individuals who remained healthy (n = 5431) versus baseline observations of healthy-to-dementia converters (n = 400); and finally, (3) baseline observations of individuals who remained MCI over time (n = 1141) versus baseline observations of MCI-to-dementia converters (n = 809).

3 | RESULTS

3.1 | General characteristics of participants

3.1.1 | Baseline groups

Individuals with MCI and dementia were significantly older compared to healthy controls ($P < 2.2e\text{-}16$, $P < 2.2e\text{-}16$, respectively), and a higher proportion of them were married ($P = 4.1e\text{-}16$, $P < 2.2e\text{-}16$, respectively) and had alcohol dependence ($P = 2e\text{-}7$, $P = 2e\text{-}18$, respectively). Univariate analysis showed that participants with MCI were more likely to suffer from various comorbidities compared to healthy controls or dementia patients (Table S1). Furthermore, a higher proportion of men suffered from MCI ($P < 2.2e\text{-}16$), whereas a higher proportion of women suffered from dementia ($P < 2.2e\text{-}16$).

3.1.2 | Progression groups

While analyzing data from progression groups, we found that 543 (8.52%) healthy individuals developed MCI over an average duration of 6.7 years, and 400 (6.27%) developed dementia over a mean period of 7 years. Additionally, 809 (41.49%) individuals with MCI developed dementia over an average of 5.5 years. Individuals who remained healthy or MCI, had follow-up data available for an average of 5.4 and 3.1 years, respectively (Table S1, Figure S1 in supporting information). The average number of visits for all the groups ranged from 3.5 to 6.7 (Table S1).

Healthy participants who progressed to MCI or dementia over time were significantly older ($P < 2.2e\text{-}16$, $P < 2.2e\text{-}16$, respectively), less educated ($P = 0.04$, $P = 0.002$, respectively), and a smaller proportion of them were married ($P = 0.002$, $P = 0.003$, respectively), compared to those who remained healthy. Additionally, those who progressed from healthy-to-MCI had a higher average of total years smoked ($P = 0.003$).

Participants who progressed from MCI-to-dementia were significantly older ($P < 0.001$), predominantly white ($P < 0.001$), more educated ($P = 0.01$), and a higher proportion of them were married ($P < 0.001$), compared to those with stable MCI diagnosis (Table S1).

3.2 | Risk factors associated with baseline and progression analyses

Adjusted odds ratios for active/inactive stages of comorbidities were measured against absence of the disease. BMI (underweight/overweight or decreasing/increasing) and GDS (mild/moderate or decreasing/increasing) categories were measured against normal or stable groups for baseline and progression analyses, respectively.

3.2.1 | Baseline versus progression analyses for healthy and MCI

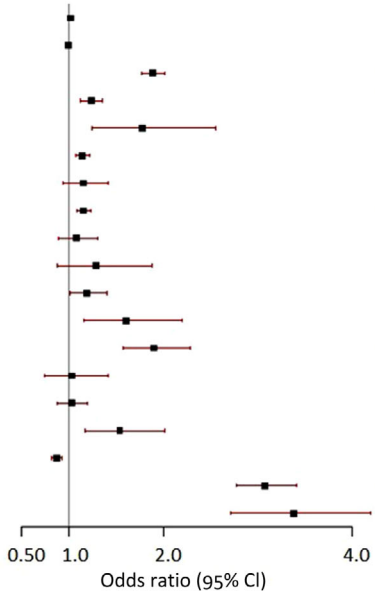
Baseline analysis, illustrated in Figure 4A, found that age (FDR $P < 0.0001$), sex (male; FDR $P < 0.0001$), active diabetes (FDR $P < 0.0001$), hypertension (FDR $P < 0.001$) and hypercholesterolemia (FDR $P < 0.001$), history of stroke (FDR $P < 0.0001$), and depression (mild and moderate; FDR $P < 0.0001$) were significantly associated with an increased risk of MCI compared to healthy individuals, while being overweight (BMI > 24.99 kg/m^2; $P < 0.001$) was significantly associated with a reduced risk of MCI. Given the progression group with individuals who remained healthy across all visits, versus those who developed MCI (Figure 4B), only age (FDR $P < 0.0001$) and increasing GDS score (from no depression to mild/moderate, or from mild to moderate; FDR $P = 0.006$) were significantly associated with an increased risk of healthy-to-MCI progression. Hence, there is a general reduction in the number of risk factors when analyzing the progression groups, compared to baseline analyses.

3.2.2 | Baseline versus progression analyses for healthy and dementia

Next, we compared baseline analysis for healthy versus dementia with progression analysis, ie, remained healthy versus healthy-to-dementia progression. As shown in Figure 5A, at baseline, age (FDR $P < 0.0001$), sex (male; FDR $P < 0.0001$), active and inactive alcohol dependence (FDR $P < 0.0001$), history of stroke (FDR $P < 0.0001$), being underweight (BMI < 18.5 kg/m^2; FDR $P < 0.001$), and depression (mild and moderate; FDR $P < 0.0001$) were significantly associated with an increased dementia risk. Moreover, being overweight (BMI > 24.99 kg/m^2; FDR $P < 0.0001$) was significantly associated

(A)

Covariates	Number of subjects		Odds ratio (95% CI)	p value	pFDR Value
	Healthy	MCI			
Age at baseline			1.024 (1.02, 1.03)	< 0.0001	< 0.0001
Total years smoked			0.998 (0.996, 1.00)	0.1029	0.4955
Male gender	4360	3353	1.89 (1.77, 2.01)	< 0.0001	< 0.0001
Active diabetes	1406	1013	1.23 (1.12, 1.36)	< 0.0001	< 0.0001
Inactive diabetes	65	65	1.78 (1.24, 2.56)	0.0018	0.0111
Active hypertension	5810	3559	1.15 (1.07, 1.23)	< 0.0001	0.0008
Inactive hypertension	301	187	1.16 (0.94, 1.42)	0.1622	0.7289
Active hypercholesterolemia	5890	3552	1.16 (1.09, 1.24)	< 0.0001	0.0002
Inactive hypercholesterolemia	360	203	1.08 (0.89, 1.31)	0.4384	1
Active alcoholism	68	55	1.29 (0.88, 1.89)	0.191	0.8047
Inactive alcoholism	385	297	1.19 (1.01, 1.41)	0.0357	0.1852
Active stroke	81	86	1.60 (1.17, 2.21)	0.0036	0.0203
Inactive stroke	224	271	1.89 (1.57, 2.29)	< 0.0001	< 0.0001
Active cardiac arrest	93	73	1.03 (0.75, 1.42)	0.8487	1
Inactive cardiac arrest	439	352	1.03 (0.88, 1.20)	0.7136	1
BMI low <18.5	138	103	1.54 (1.17, 2.02)	0.0018	0.0111
BMI high >24.9	8089	4242	0.87 (0.81, 0.93)	< 0.0001	0.0008
GDS 5-9	724	983	3.07 (2.77, 3.41)	< 0.0001	< 0.0001
GDS >9	147	222	3.38 (2.72, 4.20)	< 0.0001	< 0.0001



(B)

Covariates	Number of subjects		Odds ratio (95% CI)	p value	pFDR Value
	Remained Healthy	Healthy to MCI			
Age at baseline			1.06 (1.05, 1.07)	< 0.0001	< 0.0001
Total years smoked			1.005 (1, 1.01)	0.061	1
Male gender	1761	193	1.07 (0.89, 1.30)	0.4581	1
Active diabetes	666	82	1.22 (0.94, 1.59)	0.1364	1
Inactive diabetes	19	2	1.47 (0.33, 6.55)	0.6162	1
Active hypertension	2981	341	1.07 (0.88, 1.31)	0.485	1
Inactive hypertension	101	16	2.09 (1.17, 3.74)	0.0129	0.2899
Active hypercholesterolemia	3081	322	1.03 (0.85, 1.26)	0.7505	1
Inactive hypercholesterolemia	120	11	0.83 (0.43, 1.61)	0.5787	1
Active alcoholism	51	8	1.63 (0.75, 3.54)	0.2127	1
Inactive alcoholism	164	11	0.65 (0.35, 1.22)	0.1802	1
Active stroke	86	10	0.77 (0.39, 1.53)	0.4599	1
Inactive stroke	111	14	0.91 (0.51, 1.63)	0.7595	1
Active cardiac arrest	98	12	0.99 (0.54, 1.86)	0.993	1
Inactive cardiac arrest	221	28	0.85 (0.56, 1.30)	0.4599	1
BMI decreasing	523	74	1.26 (0.96, 1.65)	0.0944	1
BMI increasing	370	28	0.79 (0.53, 1.18)	0.247	1
GDS decreasing	210	22	1.21 (0.77, 1.92)	0.4102	1
GDS increasing	375	64	1.74 (1.30, 2.32)	< 0.0001	0.0061

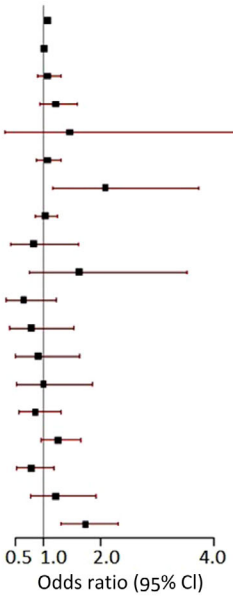
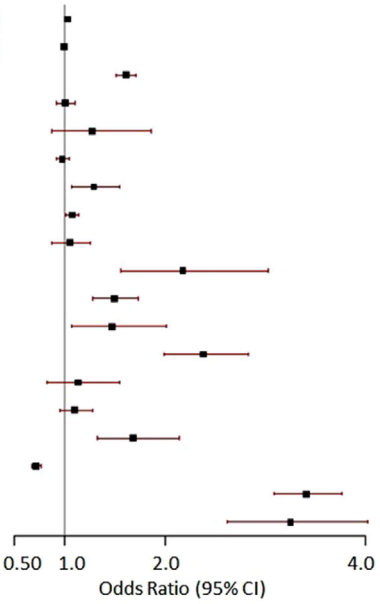


FIGURE 4 Forest plots of adjusted odds ratios for potential risk factors of baseline healthy versus mild cognitive impairment (MCI), and stable healthy versus conversion to MCI. (A), Outcome: healthy versus MCI; (B) Outcome: remained healthy versus healthy-to-MCI progression

(A)

Covariates	Number of subjects		Odds Ratio (95% CI)	p value	pFDR Value
	Healthy	Dementia			
Age at baseline			1.033 (1.029, 1.036)	< 0.0001	< 0.0001
Total years smoked			0.997 (0.995, 0.999)	0.0083	0.0509
Male gender	4360	3610	1.62 (1.52, 1.72)	< 0.0001	< 0.0001
Active Diabetes	1406	955	1.01 (0.92, 1.12)	0.8376	1
Inactive Diabetes	65	58	1.28 (0.88, 1.87)	0.2024	0.9096
Active Hypertension	5810	3879	0.98 (0.92, 1.05)	0.4979	1
Inactive Hypertension	301	267	1.3 (1.08, 1.56)	0.0066	0.0445
Active Hypercholesterolemia	5890	3923	1.08 (1.02, 1.15)	0.0205	0.1063
Inactive Hypercholesterolemia	360	258	1.06 (0.88, 1.27)	0.5754	1
Active Alcoholism	68	95	2.18 (1.57, 3.03)	< 0.0001	< 0.0001
Inactive Alcoholism	385	402	1.5 (1.29, 1.75)	< 0.0001	< 0.0001
Active Stroke	81	99	1.48 (1.08, 2.02)	0.0154	0.0866
Inactive Stroke	224	379	2.39 (2, 2.84)	< 0.0001	< 0.0001
Active Cardiac Arrest	93	83	1.14 (0.84, 1.56)	0.4234	1
Inactive Cardiac Arrest	439	421	1.11 (0.96, 1.28)	0.1833	0.8826
BMI low <18.5	138	166	1.69 (1.33, 2.15)	< 0.0001	0.0002
BMI high >24.9	8089	4504	0.72 (0.68, 0.77)	< 0.0001	< 0.0001
GDS 5-9	724	1271	3.41 (3.09, 3.77)	< 0.0001	< 0.0001
GDS >9	147	249	3.26 (2.63, 4.03)	< 0.0001	< 0.0001



(B)

Covariates	Number of subjects		Odds Ratio (95% CI)	p value	pFDR Value
	Remained Healthy	Healthy to Dementia			
Age at baseline			1.1 (1.09, 1.12)	< 0.0001	< 0.0001
Total years smoked			1 (0.99, 1.01)	0.9205	1
Male gender	1761	142	1.05 (0.84, 1.31)	0.6627	1
Active Diabetes	666	60	1.34 (0.98, 1.83)	0.0637	0.859
Inactive Diabetes	19	1	1.06 (0.12, 9.49)	0.9579	1
Active Hypertension	2981	265	1.1 (0.86, 1.39)	0.4449	1
Inactive Hypertension	101	6	1.07 (0.43, 2.63)	0.8865	1
Active Hypercholesterolemia	3081	212	0.77 (0.61, 0.97)	0.026	0.438
Inactive Hypercholesterolemia	120	5	0.52 (0.20, 1.32)	0.1692	1
Active Alcoholism	51	3	0.95 (0.28, 3.21)	0.9373	1
Inactive Alcoholism	164	9	0.88 (0.44, 1.79)	0.7319	1
Active Stroke	86	13	1.18 (0.63, 2.22)	0.5964	1
Inactive Stroke	111	14	1.09 (0.60, 1.98)	0.7701	1
Active Cardiac Arrest	98	10	1.06 (0.53, 2.12)	0.8683	1
Inactive Cardiac Arrest	221	29	1.12 (0.73, 1.72)	0.6043	1
BMI decreasing	523	66	1.48 (1.1, 1.99)	0.0097	0.218
BMI increasing	370	30	1.18 (0.78, 1.78)	0.4257	1
GDS decreasing	210	13	0.98 (0.54, 1.78)	0.9459	1
GDS increasing	375	55	1.84 (1.34, 2.54)	< 0.0001	0.0065

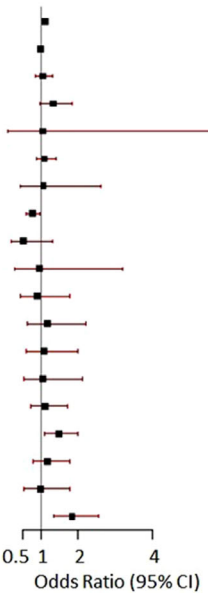


FIGURE 5 Forest plots of adjusted odds ratios for potential risk factors of baseline healthy versus dementia, and stable healthy versus conversion to dementia. (A), Outcome: healthy versus dementia; (B) Outcome: temained healthy versus healthy-to-dementia progression

with a reduced dementia risk. These results are primarily in concordance with existing literature.[1–3] In contrast, upon comparing individuals who remained healthy, to those who progressed from healthy-to-dementia, age (FDR $P < 0.0001$) and increasing GDS score (FDR $P = 0.0065$) were associated with a significantly increased risk of progressing to dementia (Figure 5B). Again, there is a general reduction in the number of risk factors when analyzing the progression groups, compared to baseline analyses. Moreover, the identified risk factors are consistent with those for healthy-to-MCI progression.

3.2.3 | Baseline versus progression analyses for MCI and dementia

We then focused on potential risk factors that were differentially associated with MCI and dementia. Figure 6 illustrates baseline (MCI vs dementia; Figure 6A) and progression analyses (remained MCI vs MCI-to-dementia; Figure 6B). At baseline, we found that age (FDR $P < 0.0001$) was significantly associated with an increased risk of having dementia. Male sex (FDR $P < 0.0001$), active diabetes (FDR $P = 0.003$) and hypertension (FDR $P = 0.002$), and being overweight (BMI > 24.99 kg/m^2; FDR $P < 0.0001$) on the other hand were associated with a reduced risk of dementia. When we considered individuals who remained MCI over time to MCI-to-dementia converters, age (FDR $P < 0.0001$) was significantly associated with increased risk of progression. Furthermore, active hypertension (FDR $P = 0.002$) was significantly associated with a reduced risk of MCI-to-dementia progression, compared to individuals with stable MCI diagnosis. The reduced number of risk factors obtained, compared to baseline analyses, was again observed.

3.3 | Sensitivity analysis

Sensitivity analysis was conducted to examine whether there were any differences between the baseline values of stable and progression groups, and if they were consistent with the progression analyses. Individuals from the progression groups were identified in the baseline samples, and subsequently non-converters were analyzed against converters.

3.3.1 | Baseline of stable healthy versus baseline of healthy-to-MCI

Baseline analysis of individuals who remained healthy over time versus those who progressed to MCI revealed significant differences between these two groups in terms of depression. Magnitude of adjusted odds ratio for depression (GDS 5–9) 1.48 ($P = 0.05$; Figure S2A in supporting information) was consistent with the progression analysis (Figure 4B).

3.3.2 | Baseline of stable healthy versus baseline of healthy-to-dementia

When we compared baseline observations of individuals who remain healthy over time to those who progressed to dementia, the magnitude of adjusted odds ratio of 1.35 ($P = 0.22$) for depression (GDS 5–9) was again consistent with the progression analysis (Figure 5B).

3.3.3 | Baseline of stable MCI versus baseline of MCI-to-dementia

Last, comparing baseline observations of individuals who remained MCI over time versus those who progressed from MCI-to-dementia, the adjusted odds ratio associated with active hypertension 0.85 ($P = 0.11$; Figure S2C), was consistent with the progression analysis (Figure 6B).

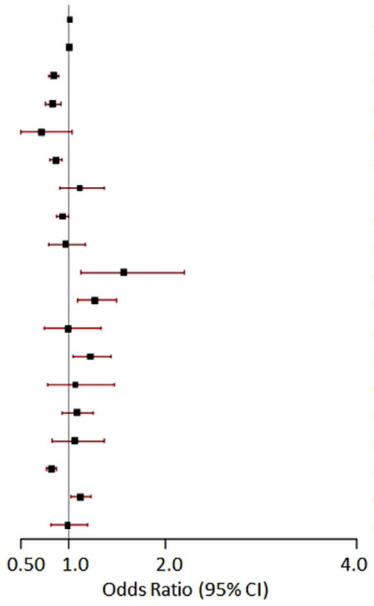
Overall, although variability in statistical significance was observed, the results from sensitivity analyses revealed similar magnitudes of effect sizes as those of the progression groups. This consistency in results increases confidence that our proposed data preparation approach is more robust and minimizes bias.

4 | DISCUSSION

In this study, we showed that when identifying risk factors for MCI and dementia, analyses based solely on baseline data (at a single time point), generally reproduce the existing findings within the literature. Specifically, among the risk factors considered in this study, the majority of significant results from baseline analyses (age, hypercholesterolemia, alcohol dependence, stroke, BMI, and depression) were in accordance with existing literature.[1–4,6,8,11–14,26,28–33] However, in some cases contrasting outcomes were observed. We report that at baseline men are at higher risk of dementia (Figure 5). Prevalence of dementia is known to be higher in women[31] due to longevity in women and faster rate of disease progression in men.[34] This may reflect inherent bias in self-selecting populations in clinical trials or research generally. However, some large population-based studies have reported no sex differences in dementia incidence, or different risk profiles for dementia progression in men and women.[35,36] In the NACC cohort, a higher proportion of men had a parent with cognitive impairment compared to women. Additionally, men had higher average of BMI and number of years of smoking, and a greater proportion of them suffered from comorbidities such as diabetes, hypercholesterolemia, history of stroke, cardiac arrest/heart attack, and alcohol dependence. Collectively, these factors might have influenced the outcomes of analyses associated with the data. These add further evidence in supporting our hypothesis that baseline analysis can be unreliable, and the outcomes may vary across different studies. Comparing MCI and dementia at baseline, active stages of diabetes and hypertension were associated with reduced dementia risk in contrast to existing literature.[1–3,6,8]

(A)

Covariates	Number of subjects		Odds Ratio (95% CI)	p value	pFDR Value
	MCI	Dementia			
Age at baseline			1.01 (1.006, 1.02)	< 0.0001	< 0.0001
Total years smoked			1.0 (0.998, 1.02)	0.844	1
Male gender	3353	3610	0.85 (0.79, 0.9)	< 0.0001	< 0.0001
Active Diabetes	1013	955	0.83 (0.76, 0.92)	0.0002	0.0027
Inactive Diabetes	65	58	0.72 (0.5, 1.04)	0.0732	0.4486
Active Hypertension	3559	3879	0.87 (0.81, 0.94)	< 0.0001	0.0017
Inactive Hypertension	187	267	1.12 (0.91, 1.37)	0.3034	1
Active Hypercholesterolemia	3552	3923	0.94 (0.87, 1.01)	0.0569	0.3836
Inactive Hypercholesterolemia	203	258	0.97 (0.79, 1.18)	0.7125	1
Active Alcoholism	55	95	1.58 (1.13, 2.21)	0.0084	0.0809
Inactive Alcoholism	297	402	1.28 (1.09, 1.5)	0.0029	0.0326
Active Stroke	86	99	0.99 (0.75, 1.34)	0.97	1
Inactive Stroke	271	379	1.23 (1.05, 1.45)	0.0132	0.1113
Active Cardiac Arrest	73	83	1.07 (0.78, 1.48)	0.6888	1
Inactive Cardiac Arrest	352	421	1.09 (0.94, 1.26)	0.2951	1
BMI low <18.5	103	166	1.07 (0.83, 1.38)	0.6221	1
BMI high >24.9	4242	4504	0.82 (0.77, 0.88)	< 0.0001	< 0.0001
GDS 5-9	983	1271	1.12 (1.03, 1.23)	0.0168	0.1259
GDS >9	222	249	0.99 (0.82, 1.19)	0.8923	1



(B)

Covariates	Number of subjects		Odds Ratio (95% CI)	p value	pFDR Value
	Remained MCI	MCI to Dementia			
Age at baseline			1.03 (1.02, 1.04)	< 0.0001	< 0.0001
Total years smoked			1 (0.99, 1.00)	0.2006	1
Male gender	587	435	1.08 (0.9, 1.31)	0.3905	1
Active Diabetes	203	104	0.80 (0.61, 1.05)	0.1125	1
Inactive Diabetes	8	5	1.23 (0.38, 4.02)	0.7266	1
Active Hypertension	705	429	0.66 (0.54, 0.81)	< 0.0001	0.00196
Inactive Hypertension	33	15	0.44 (0.22, 0.86)	0.0159	0.3573
Active Hypercholesterolemia	713	496	1.14 (0.93, 1.40)	0.2033	1
Inactive Hypercholesterolemia	23	23	1.66 (0.87, 3.17)	0.1206	1
Active Alcoholism	14	12	1.47 (0.66, 3.28)	0.3414	1
Inactive Alcoholism	72	33	0.75 (0.48, 1.17)	0.2085	1
Active Stroke	33	15	0.62 (0.33, 1.17)	0.142	1
Inactive Stroke	66	38	0.81 (0.53, 1.24)	0.3319	1
Active Cardiac Arrest	18	10	0.77 (0.35, 1.71)	0.5208	1
Inactive Cardiac Arrest	64	47	1.05 (0.69, 1.58)	0.8311	1
BMI decreasing	103	77	1.05 (0.76, 1.44)	0.7636	1
BMI increasing	53	58	1.48 (0.99, 2.19)	0.0511	0.8611
GDS decreasing	103	62	0.92 (0.65, 1.29)	0.6215	1
GDS increasing	152	98	0.99 (0.75, 1.31)	0.935	1

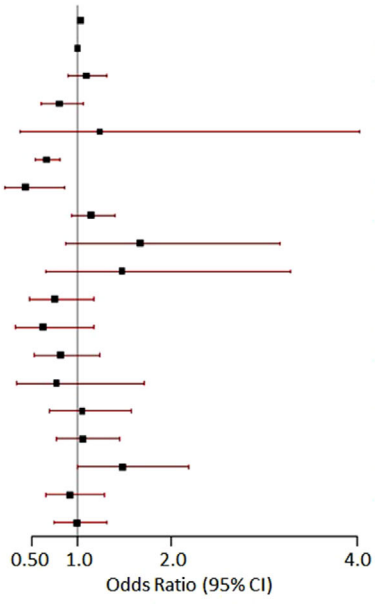


FIGURE 6 Forest plots of adjusted odds ratios for potential risk factors of baseline mild cognitive impairment (MCI) versus dementia, and stable MCI versus conversion to dementia. (A), Outcome: MCI versus dementia; (B) Outcome: remained MCI versus MCI-to-dementia progression

As opposed to the baseline approach, our proposed multi-time-point progression model highlights the features most significantly associated with cognitive decline. Cognitive status of participants and risk factors are prone to change over time, therefore risk factors measured longitudinally may have a different effect on risk associated with disease severity.[15,37–39] Additionally, collating information from multiple visits, and analyzing trends of BMI and GDS scores, better represent physiological changes over time. We found a substantially reduced number of risk factors for progression groups compared to the baseline groups. Specifically, our multi-time-point data preparation approach in assessing temporal changes in depressive symptoms shows that increased GDS score (vs stable) was significantly associated with an increased risk of healthy-to-MCI and healthy-to-dementia progression. Additionally, the proportion of stable healthy individuals (19.7%) with a clinical diagnosis of depression was significantly lower than healthy-to-MCI (35.4%) and healthy-to-dementia converters (46.5%, $P < 0.001$).

Several studies adapting varying methodologies have explored the depression-MCI/dementia relationship. Consequently, evidence exists for depression as a prodrome, a risk factor and an accompanying symptom of cognitive impairment.[15–19] A clinical study showed no relationship between the level of depression and neuropathologic markers of dementia,[40] whereas others have found common inflammatory pathology in both depression and dementia.[41] There are fewer studies on mechanism, with inconsistent findings reported.[19] In the case of MCI, a higher prevalence of depression is observed in hospital-based (vs population-based) studies,[42] highlighting the link between different diagnostic and selection criteria in different settings, and potentially contrasting outcomes. Studies analyzing the trajectory of depression (based on relapsing-remitting and number of symptoms) found varying dementia risk depending on the course of depression.[43] This indicates the importance of optimizing research design and approaches to improve reproducibility and reliability of research findings.

Despite contradictory reports, mid-life hypertension is a well-accepted risk factor for dementia.[1–3,8] However, in the present study, comparing stable MCI and MCI-to-dementia converters exhibited surprising results. Active hypertension (vs absent) was associated with a significantly reduced risk of MCI-to-dementia progression. In the case of late-life hypertension, conflicting findings have been reported so far, even in clinical trial studies that evaluated late-life antihypertensive treatment.[44] Our findings suggest that, while a history of hypertension may be associated with dementia, late-life active hypertension is associated with reduced dementia risk, compared to stable MCI. A cerebral blood-flow study suggested that in the case of essential hypertension, although there is an increase in cerebrovascular resistance, it is accompanied by a compensatory mechanism that maintains normal cerebral blood flow.[45,46] In chronic hypertension, however, changes in cerebrovascular autoregulation occurred as a result of cerebrovascular resistance. It was observed that due to the structural changes in cerebral small vessels, the limits of autoregulation were adjusted to high pressure levels. This indicated that despite the increased risk of ischemia, this adaption of the brain protects it from high intravascular pressure.[45,46] Analyzing subgroups of individuals with active hypertension based on the type of drug treatment might offer more insight[47] and will be explored in more detail in future work.

From a wider perspective, contradictory results with respect to dementia risk factors are manifold and may be explained by a combination of methodological differences. These include study design, diagnostic procedures used to determine grouping, non-standardized categorization of variables and outcomes, and selection criteria.[18,48] Moreover, factors such as variability in cohort characteristics, time of measurement, and referral patterns may also result in different estimates of dementia prevalence.[18,48]

More importantly, differences in data preparation methods, and inconsistencies in reporting of such methods in published literature, also contributes to outcome variability. Indeed, studies have shown that varying interpretations of risk factors, and relating "disease risk" to risk factors that are measured at ≤2 time points can lead to misleading results and introduce bias.[20] Therefore, in the present study we utilized a multi-time-point data preparation approach, using the NACC dataset and cardiometabolic risk factors as an exemplar, and demonstrated that few established risk factors are significantly associated with risk of progression to MCI and dementia.

A limitation of this study is the smaller sample size of progression groups, which may have led to insignificant *P*-values associated with the risk factors.[49] It is possible that depression and hypertension have larger effect sizes compared to the other risk factors analyzed in this study, hence they were identified as significant variables in both the baseline and progression analyses. Therefore, there is a need for large population studies from birth cohorts, which would be invaluable to better understand the relationship of different risk factors throughout the lifecycle. Further, we have investigated all-cause dementia and not specific dementia subtypes, such as Alzheimer's disease or vascular dementia, and this might potentially have led to some mixing effects. Further work should focus on specific diseases to reduce such effects, and application to other dementia datasets to validate our approach. Moreover, it is worth exploring risk factors associated with alternating diagnoses to identify which significant factors emerge. This will in turn help us understand the similarities and differences in disease progression between stable and unstable converters.

Overall, our proposed multi-time-point data preparation approach in analyzing risk factors for neurological disorders, such as dementia, may provide more robust and reproducible results, which are urgently needed in current biomedical and clinical research.[50] Subsequently, this approach can also be adapted in other scientific fields.

ACKNOWLEDGMENTS

This project was supported by the European Union's INTERREG VA Programme, managed by the Special EU Programmes Body (SEUPB [Centre for Personalised Medicine, IVA 5036]), with additional support by the Northern Ireland Functional Brain Mapping Project Facility (1303/101154803), funded by invest Northern Ireland and the University of Ulster (KongFatt Wong-Lin), Alzheimer's Research UK (ARUK) NI Pump Priming (Magda Bucholc, Stephen Todd, KongFatt Wong-Lin, Paula L. McClean), Ulster University Research Challenge Fund (Magda Bucholc, Stephen Todd, KongFatt Wong-Lin), the Dr George Moore

Endowment for Data Science at Ulster University (Magda Bucholc), and the COST Action Open Multiscale Systems Medicine (OpenMultiMed) supported by COST (European Cooperation in Science and Technology; KongFatt Wong-Lin). The views and opinions expressed in this article do not necessarily reflect those of the European Commission or the SEUPB.

The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

We would like to acknowledge the efforts of our colleague Niamh McCombe, PhD researcher at Ulster University, for proofreading this article.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Edwards Iii GA, Gamez N, Escobedo GJ, Calderon O, Moreno-Gonzalez I. Modifiable risk factors for Alzheimer's disease. *Front Aging Neurosci*. 2019;11:146.
2. Deckers K, van Boxtel MPJ, Schiepers OJG, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry*. 2015;30:234-246.
3. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement (N Y)*. 2015;11:718-726.
4. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn Disord*. 2009;28:75-80.
5. Mielke MM, Zandi PP, Shao H, et al. Gustafson, The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology*. 2010;75:1888-1895.
6. Crowe M, Sartori A, Clay OJ, et al. Diabetes and cognitive decline: investigating the potential influence of factors related to health disparities. *J Aging Health*. 2010;22:292-306.
7. Sano M, Zhu CW, Grossman H, Schimming C. Longitudinal cognitive profiles in diabetes: results from the National Alzheimer's Coordinating Center's Uniform Data. *J Am Geriatr Soc*. 2017;65:2198-2204.
8. Bermejo-Pareja F, Benito-Leon J, Louis ED, et al. Risk of incident dementia in drug-untreated arterial hypertension: a population-based study. *J Alzheimer's Dis*. 2010;22:949-958.
9. Corrada MM, Hayden KM, Paganini-Hill A, et al. Age of onset of hypertension and risk of dementia in the oldest-old: the 90+ Study. *Alzheimers Dement (N Y)*. 2017;13:103-110.
10. Qizilbash N, Gregson J, Johnson ME, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol*. 2015;3:431-436.
11. Ilomaki J, Jokanovic N, Tan ECK, Lonnroos E. Alcohol consumption, dementia and cognitive decline: an overview of systematic reviews. *Curr Clin Pharmacol*. 2015;10:204-212.
12. Rehm J, Hassan O, Black SE, Shield KD, Schwarzinger M. Alcohol use and dementia: a systematic scoping review. *Alzheimers Res Ther*. 2019;11:1.
13. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS ONE*. 2015;10:e0118333.
14. Tyas SL, White LR, Petrovitch H, et al. Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging*. 2003;24:589-596.
15. Muliyala KP, Varghese M. The complex relationship between depression and dementia. *Ann Indian Acad Neurol*. 2010;13:S69-73.
16. Wiels W, Baeken C, Engelborghs S. Depressive Symptoms in the elderly-an early symptom of dementia? A systematic review. *Front Pharmacol*. 2020;11:34.
17. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? *Maturitas*. 2014;79:184-190.
18. Panza F, Frisardi V, Capurso C, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? *Am J Geriatr Psychiatry*. 2010;18:98-116.
19. Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. *Curr Opin Psychiatry*. 2011;24:461-472.
20. Frost C, White IR. The effect of measurement error in risk factors that change over time in cohort studies: do simple methods overcorrect for 'regression dilution'? *Int J Epidemiol*. 2005;34:1359-1368.
21. Moore PJ, Lyons TJ, Gallacher J, Alzheimer's Disease Neuroimaging Initiative. Using path signatures to predict a diagnosis of Alzheimer's disease. *PLoS ONE*. 2019;14:e0222212.
22. Baker E, Iqbal E, Johnston C, et al. Trajectories of dementia-related cognitive decline in a large mental health records derived patient cohort. *PLoS ONE*. 2017;12:e0178562.
23. Ding X, Bucholc M, Wang H, et al. A hybrid computational approach for efficient Alzheimer's disease classification based on heterogeneous data. *Sci Rep*. 2018;8:9774.
24. Beekly DL, Ramos EM, van Belle G, et al. NIA-Alzheimer's Disease Centers, The National Alzheimer's Coordinating Center (NACC) Database: an Alzheimer disease database. *Alzheimer Dis Assoc Disord*. 2004;18:270-277.
25. Jefferson AL, Beiser AS, Himali JJ, et al. Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham Heart Study. *Circulation*. 2015;131:1333-1339.
26. Shi L, Morrison JA, Wiecha J, Horton M, Hayman LL. Healthy lifestyle factors associated with reduced cardiometabolic risk. *Br J Nutr*. 2011;105:747-754.
27. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann Stat*. 2001;29:1165-1188.

28. Guerreiro R, Bras J. The age factor in Alzheimer's disease. *Genome Med*. 2015;7:106.
29. Ganguli M, Fu B, Snitz BE, Hughes TF, Chang CH. Mild cognitive impairment: incidence and vascular risk factors in a population-based cohort. *Neurology*. 2013;80:2112-2120.
30. Bachman DL, Wolf PA, Linn R, et al. Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. *Neurology*. 1992;42:115-119.
31. Berr C, Wancata J, Ritchie K. Prevalence of dementia in the elderly in Europe. *Eur Neuropsychopharmacol*. 2005;15:463-471.
32. Anttila T, Helkala E, Viitanen M, et al. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *BMJ*. 2004;329:539.
33. Viswanathan A, Macklin EA, Betensky R, Hyman B, Smith EE, Blacker D. The influence of vascular risk factors and stroke on cognition in late life: analysis of the NACC Cohort. *Alzheimer Dis Assoc Disord*. 2015;29:287-293.
34. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry*. 2013;28:1109-1124.
35. Artero S, Ancelin ML, Portet F, et al. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry*. 2008;79:979-984.
36. Ruitenberg A, Ott A, van Swieten JC, Hofman A, Breteler MM. Incidence of dementia: does gender make a difference? *Neurobiol Aging*. 2001;22:575-580.
37. Willett W. An overview of issues related to the correction of nondifferential exposure measurement error in epidemiologic studies. *Stat Med*. 1989;8:1031-1040.
38. Cain KC, Kronmal RA, Kosinski AS. Analysing the relationship between change in a risk factor and risk of disease. *Stat Med*. 1992;11:783-797.
39. Knuiman MW, Divitini ML, Buzas JS, Fitzgerald PE. Adjustment for regression dilution in epidemiological regression analyses. *Ann Epidemiol*. 1998;8:56-63.
40. Wilson RS, Capuano AW, Boyle PA, et al. Clinical-pathologic study of depressive symptoms and cognitive decline in old age. *Neurology*. 2014;83:702-709.
41. Leonard BE. Inflammation, depression and dementia: are they connected? *Neurochem Res*. 2007;32:1749-1756.
42. Ismail Z, Elbayoumi H, Fischer CE, et al. Prevalence of depression in patients with mild cognitive impairment: a systematic review and meta-analysis. *JAMA Psychiatry*. 2017;74:58-67.
43. Mirza SS, Wolters FJ, Swanson SA, et al. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry*. 2016;3:628-635.
44. Oveisgharan S, Hachinski V. Hypertension, executive dysfunction, and progression to dementia: the canadian study of health and aging. *Arch Neurol*. 2010;67(2):187-192.
45. Kety SS, Hafkenschiel JH, Jeffers WA, Leopold IH, Shenkin HA. The blood flow, vascular resistance, and oxygen consumption of the brain in essential hypertension. *J Clin Invest*. 1948;27:511-514.
46. Kety SS, Schmidt CF. Cerebral blood flow and cerebral oxygen consumption in five patients with hypertension. *Am J Med Sci*. 1946;212:124.
47. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*;2009(4):2009.
48. Ganguli M, Kukull WA. Lost in translation: epidemiology, risk, and Alzheimer disease. *Arch Neurol*. 2010;67:107-111.
49. Thiese MS, Ronna B, Ott U. P value interpretations and considerations. *J Thorac Dis*. 2016;8:E928-E931.
50. Baker M. 1,500 scientists lift the lid on reproducibility. *Nature*. 2016;533:452-454.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kaur D, Bucholc M, Finn DP, Todd S, Wong-Lin K, McClean PL. Multi-time-point data preparation robustly reveals MCI and dementia risk factors. *Alzheimer's Dement*. 2020;12:e12116.
https://doi.org/10.1002/dad2.12116