1.a. Full Title:
Impact of vascular factors on the trends in dementia incidence

b. Abbreviated Title (Length 26 characters):
CV factors and dementia trends

2. Writing Group:
Core writing group members: Chi-Hun Kim, Lenore Launer, John Gallacher, Christoph Jindra, Catherine Calvin, Graciela Muniz Terrera, Rebecca Gottesman, Melinda Power and others from collaborating cohorts (TBN)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _CHK_ [please confirm with your initials electronically or in writing]

First author: Chi-Hun Kim
Address: Department of Psychiatry, Warneford Hospital, University of Oxford, OX3 &JX Oxford, UK
Phone: +44(0)1865 613192 Fax: NA
E-mail: chi-hun.kim@psych.ox.ac.uk

ARIC authors to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Rebecca F. Gottesman
Address: Phipps 446D; Johns Hopkins University School of Medicine 600 North Wolfe Street; Baltimore, MD 21287
Phone: (410) 614-2381 Fax: (410) 955-0672
E-mail: rgottesm@jhmi.edu

3. Timeline: March 2019 – December 2021
4. **Rationale:**

Dementia is a global health problem for which there is no disease modifying therapy (Prince et al, 2015). Encouragingly, several population-based cohort studies have reported a declining incidence of dementia in the UK, US and European countries (Schrijvers et al, Neurology, 2012; Matthews et al., Nature Comms., 2016; Grasset et al, Alz. & Dem., 2016; Satizabal et al, NEJM, 2016; Ahmadi-Abhari et al, BMJ, 2017). Changes in prevalence and treatment of vascular factors such as hypertension are suspected as major determinants of this trend. However the evidence for this is inconclusive as estimates for the impact of vascular factors on the declining incidence of dementia vary widely between studies, ranging from ‘no significant modification’ (Satizabal et al, 2016) to ‘accounting for about 25%’ (Ahmadi-Abhari et al, 2017).

There are potential reasons for these inconsistent results. First, the previous studies are prone to selection bias before study enrolment (Mayeda et al, IJE, 2018) as they have analysed people who were 60 years old or older, i.e. late-life cohorts. For example, people who are susceptible to mid-life exposure to smoking will be depleted by 60 years of age as they may die early or become too ill to participate in late-life cohort studies. The latter group who are not in the study but alive (Drop-outs from Mid-life cohorts in the Figure) may develop more dementia, and the smokers remained in the study may have more protective factors than the non-smokers. As a result, analysing only older participants enrolled into or remained in the study can underestimate not only dementia incidence itself but also the impact of vascular factors on dementia (Hernán et al, Epidemiology, 2008). Second, the previous studies have used different analytical methods, which makes it difficult to compare results from multiple studies. Lastly, single cohort studies may not have enough statistical power.

To better estimate the impact of vascular factors on the declining incidence of dementia, we propose to conduct pooled analyses using eight population-based prospective cohorts with mid-life (40+ years of age) vascular exposures and dementia outcomes. We will also use consistent analytical methods across cohorts, which can account for the selection bias issue.

5. **Main Hypothesis/Study Questions:**
Research Question: How much of the changing incidence of dementia is attributable to vascular factors?

# Brief summary of eight cohorts that will be used in the project

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>Age at baseline</th>
<th>Data period</th>
<th>Midlife vascular factors</th>
<th>Dementia diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis Risk in Communities study</td>
<td>15792</td>
<td>44-66</td>
<td>1987-2013</td>
<td>Yes</td>
<td>Expert panel</td>
<td></td>
</tr>
<tr>
<td>AGES-Reykjavik Study</td>
<td>30795</td>
<td>32-60</td>
<td>1967-2011</td>
<td>Yes</td>
<td>Expert panel</td>
<td></td>
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<tr>
<td>Honolulu-Asia Aging Study</td>
<td>8006</td>
<td>45-68</td>
<td>1965-2011</td>
<td>Yes</td>
<td>Expert panel</td>
<td>Male only</td>
</tr>
<tr>
<td>Framingham Heart Study</td>
<td>15338</td>
<td>5-85</td>
<td>1948-2015</td>
<td>Yes</td>
<td>Expert panel</td>
<td></td>
</tr>
<tr>
<td>Caerphilly Prospective Study</td>
<td>2959</td>
<td>42-61</td>
<td>1979-2004</td>
<td>Yes</td>
<td>Expert panel</td>
<td>Male only</td>
</tr>
<tr>
<td>English Longitudinal Study of Ageing</td>
<td>17906</td>
<td>50+</td>
<td>2002-2017</td>
<td>Yes</td>
<td>Algorithmic</td>
<td></td>
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<tr>
<td>National Study of Health and Development</td>
<td>5362</td>
<td>Birth</td>
<td>1946-2015</td>
<td>Yes</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Stress and Health Study</td>
<td>10308</td>
<td>35-55</td>
<td>1985-2016</td>
<td>Yes</td>
<td>*</td>
<td>Civil servants</td>
</tr>
</tbody>
</table>

* We will develop algorithmic diagnoses

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

*Study design
A cross-cohort study with the eight population-based prospective cohorts

*Inclusion/exclusion criteria
All ARIC participants

*Variables (From Exam 1 to Exam 5/NCS)
- Outcomes: all-cause dementia, subtypes of dementia (AD or VaD), date(or year) of diagnosis
- Exposures: diabetes (diagnosis, blood glucose, antidiabetics), hypertension (diagnosis, systolic and diastolic blood pressure, antihypertensives), hyperlipidemia (blood total cholesterol, lipid-lowering drugs), coronary heart disease (diagnosis,
antiplatelet/anticoagulant), stroke (diagnosis), smoking (category(never, former, current) and pack-year), obesity (BMI, weight, height)

- Covariates: age at exams, sex, race, education (study defined category), socioeconomic status (e.g. study defined job class), alcohol use (category(never, former, current) and g/week), physical activity(study defined), APOE genotyping (number of e2/e3/e4)
- Administrative: subject ID, cohort, date(or year) of birth, death and exams

*Analysis Plan
For cohort-specific analyses, we will
- Harmonize individual variables across cohorts. For example, education categories will be matched to the International Standard Classification of Education (ISCED) 1997. Diabetes will be defined as a fasting glucose level of at least 126 mg/dL, a nonfasting glucose of at least 200 mg/dL, self-report of physician diagnosed diabetes, or use of oral diabetes medications or insulin.
- Calculate the incidence of dementia across calendar years after accounting for covariates and informative drop-outs using inverse probability weighting
- Estimate the impact of vascular factors on dementia incidence after accounting for covariates and informative drop-outs. We will use g-methods which can take into account time-varying exposure and confounder feedback and allow researchers to test hypothetical intervention scenarios (Naimi et al, IJE, 2017). Interaction analyses will be performed using birth year group, age group, gender, education, race and APOE genotyping.
- Estimate the impact of vascular factors to the trends in dementia by using the models built above. We will test several hypothetical intervention scenarios on vascular exposures, e.g. if smoking pattern had not changed over time what would have been the trends of dementia incidence? Stratification analyses will be performed using birth year group, age group, gender, education, race and APOE genotyping.
- Conduct sensitivity analyses to check the impact of the selection bias by comparing estimates with and without accounting for informative drop-outs.

For pooled analyses,
- Before pooling, we will assess heterogeneity among the estimates from each cohort by visual inspection of forest plots and statistical tests using Chi-squared and I² statistics.
- If the heterogeneity is within reasonable limits (e.g. I² less than 60%), we will conduct pooled analyses using either random or fixed effect models. If the heterogeneity is substantial, we will evaluate the sources of the heterogeneity and will stratify our analyses across the cohorts based on age group, birth year group, sex, education, APOE genotyping, race and country.

7.a. Will the data be used for non-CVD analysis in this manuscript? __x__ Yes  ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? __x__ Yes  ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)
8.a. Will the DNA data be used in this manuscript?  ____ Yes    _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes   ____ No NA

The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:  
http://www.cscc.unc.edu/ARIC/search.php

____X__ Yes   _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Gottesman et al., JAMA Neurology, 2017 “Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort”

Knopman et al., Alzheimer’s & Dem., 2016 “Mild cognitive impairment and dementia prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes    _X_ No

11.b. If yes, is the proposal

___  A. primarily the result of an ancillary study (list number* __________

___  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at  
http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms.  
http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.