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Research paper

# Cardiovascular risk factors and risk of incident depression throughout adulthood among men: The Johns Hopkins Precursors Study



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## ABSTRACT

*Background:* Modifiable cardiovascular risk factors elevate risk of subsequent depression in older adults, but the effect of their onset before or after age 65 on incident depression is unclear.

*Methods:* Participants were 1190 male medical students without a diagnosis of depression, who matriculated in 1948–1964 and followed through 2011. Cox proportional hazards models were used to assess associations of vascular risk-factor burden, diabetes, hypertension, hyperlipidemia, smoking status, and overweight/obese status with onset of incident depression. Adjustment covariates were race, enrollment wave, baseline age, physical activity, and heavy alcohol use.

*Results:* The analysis included 44,175 person-years of follow-up. Among participants depression-free until age 65, vascular risk-factor burden after age 65 (Hazard Ratio, [HR]: 2.13, 95% Confidence Interval, [CI]: 1.17, 3.90) was associated with incident depression risk after age 65. The magnitude of vascular risk-factor burden after age 65 on depression risk after age 65 is comparable to the effect of 8.2 additional years of age. Diabetes (HR: 2.79, 95% CI: 1.25, 6.26), hypertension (HR: 2.72, 95% CI: 1.52, 4.88), and hyperlipidemia (HR: 1.88, 95% CI: 1.05, 3.35) before age 65 were associated with incident depression risk after age 65. Men diagnosed with diabetes after age 65 had 2.87 times the risk of incident depression after age 65 (95% CI: 1.24, 6.62). *Limitations:* Our findings are restricted to male former medical students, which may affect study generalizability.

*Conclusions:* Results support the vascular depression hypothesis. Depression screening in older adults with vascular risk-factor burden may provide an avenue for prevention of late-onset depression.

#### 1. Introduction

Cardiovascular disease (CVD) is a common, growing public health challenge given increases in the older segments of the US population (Go et al., 2013). In 2013, 83.6 million Americans had one or more CVD, of whom 42.2 million were 60 years of age or older (Go et al., 2013). Prior research suggests CVD and depression have a reciprocal relationship: each increases the risk of developing the other (Alexopoulos, 2010; Alexopoulous et al., 1997; Barnes et al., 2012; Newberg et al., 2006). Despite being a top contributor to disability (García-Peña et al., 2013) and cognitive impairment (Diniz et al., 2013), depression in older adults is often undertreated (Licht-Strunk et al., 2009). The vascular depression hypothesis has been used to explain how CVD promulgates late-onset depression (Alexopoulous et al., 1997). Cardinal features of late-onset depression, here taken to indicate depression with incidence after age 65, are diagnosis of incident depression at age 65 and older and presence of vascular disease or cardiovascular risk factors (Alexopoulous et al., 1997). Secondary features include greater psychomotor disturbance, apathy, executive dysfunction, lesions in basal ganglia, and white matter hyperintensities (Thomas et al., 2004). Modifiable cardiovascular risk factors include diabetes mellitus, hypertension, hyperlipidemia, obesity, and smoking (Barnes and Yaffe, 2011). The influence of cardiovascular risk factors on incident depression is likely more pronounced in older adults than in middle-aged or younger adults, due to underlying physiological

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**Fig. 1.** Conceptual framework for the analysis. The dotted line illustrates the association of cardiovascular risk factors occurring before age 65 and the onset of incident depression up to age 65, using the full cohort. The solid lines show the association between cardiovascular risk factors occurring before age 65 or at and after age 65 and the onset of incident depression at and after age 65, using a subset of the cohort who survived up to age 65. Cardiovascular risk factors occurring after the onset of incident depression were excluded from the analysis. We used the cutoff of age 65 since onset after age 65 years was one of the cardinal features of vascular depression.

mechanisms (Taylor et al., 2013).

Previous studies of associations of midlife cardiovascular risk factors and late-onset depression have used cohorts with short durations of follow-up or follow-up without repeated measurement of midlife cardiovascular risk factors (Barnes et al., 2012; Sheline et al., 2006). The present investigation addresses these limitations by leveraging high-quality prospectively collected data on cardiovascular risk factors and depression from a long-standing cohort with extensive follow-up. The study is well-suited to examine cardiovascular risk factors occurring before vs. after age 65 and diagnosis of incident depression.

We evaluated the timing during life of the occurrence of modifiable cardiovascular risk factors and determined the extent to which they are associated with subsequent development of incident depression. Pursuant to the vascular depression hypothesis, we hypothesized vascular risk factor burden and cardiovascular risk factors occurring before age 65 are associated with increased risk of developing incident depression after age 65, not before age 65. We examined this hypothesis using data up to age 65 to examine the association of cardiovascular risk factors with incident depression before age 65. Among participants who survived depression-free up to age 65, we determined whether the presence of cardiovascular risk factors occurring before vs. after age 65 was associated with onset of incident depression after age 65 (Fig. 1).

## 2. Methods

#### 2.1. The Johns Hopkins Precursors Study

The Johns Hopkins Precursors Study, initiated in 1946, enrolled 1337 medical school students in matriculating classes from 1948 to 1964 of The Johns Hopkins School of Medicine. Participants are followed approximately annually through mailed questionnaires to update morbidity and exposure information (Fig. 2). The average 5-year period response rate is 90% (range 87–94%). Vital status is known for over 99% of the cohort. Self-reports of body mass index (BMI) and systolic blood pressure (SBP) have been validated externally (Klag et al., 1993). Study procedures are reviewed regularly and approved by the Johns Hopkins University School of Medicine Institutional Review Board.

We aimed to examine incident depression, hence excluded participants diagnosed with clinical depression before graduating from medical school (N=16), and those with no follow-up (N=9). The final sample size for this study was N=1190 participants.

#### 2.2. Incident depression

The primary outcome was first diagnosis of depression. Participants or family members submitted approximately annually mailed questionnaires inquiring about medical and psychiatric conditions in a checklist (Chang et al., 1997; Ford et al., 1998). Also, they answered questions about use of antidepressant medication multiple times and lifetime history of receiving care from a mental health specialist for *an emotional problem* in 1988 (Chang et al., 1997; Ford et al., 1998). Depression before medical school graduation were ascertained by history and physical examination, review of student health records for information about treatment and hospitalization for depression, and exit interviews with specific questions about depressive symptoms. Those who committed suicide were included in the case definition of depression.

Additionally, a committee of physician reviewers, unaware of the study's hypothesis, adjudicated diagnoses alongside age of onset after reviewing participant self-reports (Chang et al., 1997; Ford et al., 1998). Strict adherence to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* was not possible, so the term, major depression, is not used. Questions about depression treatment assessed validity of the diagnosis of clinical depression (Chang et al., 1997; Ford et al., 1998).



**Fig. 2.** Brief timeline of data collection in the Johns Hopkins Precursors Study. Diagnoses for morbidities, cardiovascular disease, hypertension, and depression, were assessed approximately annually after graduation from medical school. Data about health behaviors (body mass index (BMI), blood pressure (BP) measurements) and habits (smoking status and frequency of alcohol consumption) were assessed at enrollment into the study around medical school graduation. These characteristics were assessed every five years from 1966 to 1984. After 1984, BMI and BP measurements were assessed in 1985, 1988, 1993, 1998, 2001 (BMI only), 2002, 2003, and 2006. Hypertension was defined as self-reported blood pressure  $\geq 160/95$  mm Hg on one annual questionnaire,  $\geq 140/90$  mm Hg on  $\geq 2$  annual questionnaires, or as hypertension requiring drug therapy.(Klag et al., 2002; Wang et al., 2008) Participants self-reported multiple blood pressure readings varying from one to seven per questionnaire on approximately annual questionnaires, so an average of the SBPs was taken for each age of reported blood pressures. After 1984, habits were assessed in 1986, 1989, 1993, 1993, 1997, 2000, 2003, and 2006. Blood draw measures consisted of a complete blood panel with measures on total and HDL cholesterol. Total cholesterol was collected during medical school and in 2007–2008. HDL cholesterol was only collected in 2007–2008.

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