**Introduction**

Hypertension is known for being consistently linked to physical health conditions including cardiovascular disease and coronary artery disease1, but it is also a major risk factor for mental conditions like early cognitive decline, vascular dementia, and possibly Alzheimer’s disease2. Moreover, some of hypertension’s negative impacts on cognitive function have known causal pathways: hypertension disrupts cerebral blood vessel structure and function, and encourages stroke in critical white matter regions3. Both hypertension and dementia are on the rise3, 4, yet while hypertension associated cognitive impairment can range in symptoms and severity, the impacts of hypertension treatments and co-morbid conditions on cognitive function are not well known.

Cognitive ageing is a normal, but important aspect of healthy ageing. Accelerated cognitive decline, however, is association with lower well-being, higher morbidity and mortality, and as cognitive function worsens, dementia develops 5. Moreover, the current body of evidence suggests that while hypertension in midlife impacts later cognitive function, strong pre-morbid cognitive function can protect an individual against a host of physical ailments later in life6, 7, including hypertension8, and related stroke and coronary artery events9, 10.

Gender and biological sex differences have known impacts on cardiovascular health. Men have been more likely to develop cardiovascular conditions than women11, a major reason why men have been the subject of more intervention studies than women. Nevertheless, cardiovascular disease is the leading cause of death in women as well as men12. Biological sex impacts hypertension differently for men and women, e.g. through hormones and gene dosage from the sex chromosomes, and these differences are conserved across different countries and ethnic groups13. Additionally, typical gender roles are associated with men behaving in ways that increase their health risks.14

Previous work on cardiovascular events found an interaction between biological sex and cognitive function: women with higher cognitive function early in life were less likely to experience coronary disease or stroke9. Socioeconomic factors, in particular education, have been implicated as mediators in the relationship between cognitive function, sex, and cardiovascular health. We hypothesized that hypertension, a wide-spread condition related to cardiovascular and mental health, could also be predicted by an interaction between early life cognitive function and biological sex, as well as socioeconomic indicators. We tested these hypotheses using the US National Longitudinal Survey of Youth 1979 (NLSY79).

**Methods**

*Participants*

The NLSY79 was initially sampled from non-institutionalized people aged 14-21, living in the United States. The study consisted of 12,686 original participants, and was ethnically representative of the population at the time; 16% of participants were Latino, 25% were Black, and 59% were neither Black nor Latino.

The initial interview took place in 1979, and respondents were re-interviewed annually until 1994, and biennially after. The most recent data come from the 2014 survey. A description of the variables used is presented in Table 1.

*Hypertension diagnosis*

3,101 cases of hypertension were diagnosed by the end of 2016. 9,585 individuals were either never diagnosed with hypertension or did not complete any survey that collected hypertension diagnosis data. These cases were censored as not being diagnosed. 4 individuals refused to answer questions about hypertension diagnosis, and were also censored as not being diagnosed. 3 individuals were recorded as having hypertension since birth, and their records were removed from further analyses. Month and year of diagnosis was available for cases of hypertension, and these were used to create event dates. Survival data were thus constructed as starting at birth and ending at the time of hypertension diagnosis, or being censored at the most recent date of data collection or whenever the individual last participated in the study.

*Cognitive function*

General cognitive function was assessed in the NLSY79 via the Armed Forces Qualifications Test (AFQT), specifically the 1989 renormed version. The test was given in 1980, when all participants were between 15 and 23 years of age; these tests scores can be used to reflect pre-morbid cognitive function. The scores were derived from ten subtests that assessed arithmetic reasoning, mathematical knowledge, work knowledge, and paragraph comprehension. The AFQT is a valid and reliable measure of cognitive function, having been associated with outcomes including academic achievement and job performance15, 16. To be consistent with previous work in this sample8, 17, we used the z-scored AFQT percentile score, taken from The Bell Curve website18.

*Covariates*

Sex was originally determined by observation, and if it was not obvious, participants were asked directly by the interviewer during the initial survey in 1979. Every case was checked, and in 45 cases corrected, by the National Opinion Research Center in 1986.

Several variables were incorporated as controls into progressive models; these include the age in childhood when the first interview was conducted in 1979, childhood socioeconomic status (SES) and adult SES. The SES variables were both averages of different z-transformed income, education, and occupation status variables18. To calculate childhood SES, parents’ information was used; to calculate adult SES, individuals’ information from surveys in 2012 [@CW: is this true for all three?] were used. A higher SES indicates more socioeconomic advantage.

The adult income variable was the total net family income in the past year, which was also log and z-transformed to be consistent with earlier work8, 18. Net income for the individual was also available in the dataset, and transformed the same way as family income. Adult education was the highest grade completed. Occupation status was derived as a continuous variable using an updated version of the Duncan Socioeconomic Index19, 20.

*Analyses*

All analyses were conducted using accelerated failure time regression models, a form of survival analysis that is fully parametric and not limited by the assumption of proportional hazard modeling.21 Different cases were missing values depending on which covariates were included. Complete case and multiply imputed analyses yielded the same findings in previous work,8 so only complete cases were analysed.

Seven accelerated failure time (AFT) regressions were modeled. The outcome of AFT models were the event of a hypertension diagnosis, and if such a diagnosis was given, the date of the diagnosis, accurate to the month. The log-logistic distribution was used as the linking error distribution in all models because it consistently produced better fit than the alternatives. The first model was our base model, and included cognitive function, sex, and childhood age. The second model introduced an interaction between sex and cognitive function. Model three added childhood SES as a covariate, and model 4 added adult SES to model 3. Since adults SES is composed of distinct subcomponents, income, education and occupation status, there is a precedent analyse the effect of each of these variables independently8. Models 5 through 7 broke down adult SES into its constituent parts, adding each in isolation to model 3 to examine the effects of adults SES in greater detail.

**Results**

Kaplan-Meier survival curves were plotted to depict the interaction between cognitive function and sex, and the relationship with hypertension diagnosis (Figure 1). When cognitive function was divided into tertiles and combined with sex, clear differences emerged. Overall, there appeared to be an interaction between the female sex and cognitive function, such that lower functioning men were less likely to receive hypertension diagnoses than lower functioning women, whereas higher functioning women were considerably less likely to be diagnosed with hypertension than higher functioning men.

This association was formally confirmed in our AFT models (Table 2), which yielded a significant interaction between sex and cognitive function. Adding childhood SES had no effect on this association, and was not itself a significant predictor of hypertension diagnosis. Adding adult SES did attenuate the interaction, though it remained significant. Adult SES was itself significant as well; higher SES individuals were less likely to be diagnosed with hypertension.

Of the adult SES subcomponents, none were significant except income (Table 3), though even in this model, the sex and cognitive function interaction remained significant. When a sex and income interaction was also introduced, the sex and cognitive function interaction was attenuated and no longer significant.

It seemed counter-intuitive that income would be a significant predictor, but not occupational status, since the two are closely linked. However,

**Discussion**

This study investigated the association of hypertension development with sex, pre-morbid cognitive function, and the interaction of these two variables. Our results show that sex and cognitive function reliably interact to predict hypertension diagnoses. Women with higher cognitive function are less likely to develop hypertension than higher functioning men, and the opposite is true at the other end of the spectrum: lower functioning women are more likely to develop hypertension than lower functioning men.

Childhood SES did not explain the effects of the interaction, nor did it appear to otherwise be related to hypertension diagnosis. Adult SES did predict hypertension diagnosis, such that higher SES individuals were less likely to become hypertensive. We tested the individual constituent variables of adult SES in order to determine if any of the constituents were particularly important. As a result, we found that the adult SES effect could be explained by the income component of SES, thus, individuals with higher income were less likely to develop hypertension. Income alone did not affect the sex and cognitive function interaction, but including an interaction between and sex and income did. This suggests that the segment of higher functioning women, who are less likely to become hypertensive, overlaps with the segment of higher earning women, who also are less likely to become hypertensive.

Higher functioning women in this sample also tended to have a higher income later in life. Thus, it is difficult to say whether this segment of women benefitted more from having higher cognitive function, or more from having a higher income. There is evidence to support both explanations.

The income variable represents family income, which makes it impossible to disentangle the effects of working from

from having higher cognitive function

Lawlor et al. found similar results, but in their analyses, the cognitive function x sex interaction could be explained by education, not income. Even at the genetic level, less education was associated with greater risk for high blood pressure 22

After the age of 70, women had a higher prevalence of

hypertension across all racial groups

NHANES II [26] and

NHANES III [27] suggest that the rate of the age-associated

increase in blood pressure accelerates in women

around the fifth and sixth decades of life and eventually

exceeds that of men (Figure 2)

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