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Glucose levels during life and neuropathologic findings at autopsy among people never treated for diabetes

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ABSTRACT

We evaluated associations between glucose and dementia-related neuropathologic findings among people without diabetes treatment history to elucidate mechanisms of glucose's potential effect on dementia. We used glucose and hemoglobin A1c values to characterize glucose exposures over 5 years before death (primary) and age bands from 55–59 through 80–84 (secondary). Autopsy evaluations included Braak stage for neurofibrillary tangles, Consortium to Establish a Registry for Alzheimer's Disease grade for neuritic plaques, macroscopic infarcts including lacunar infarcts, Lewy bodies, cerebral microinfarcts, and hippocampal sclerosis. Of 529 who came to autopsy, we included 430 with no history of diabetes treatment. We found no associations between glucose levels and Braak stage or Consortium to Establish a Registry for Alzheimer's Disease grade. There was a suggestion of a relationship between glucose and hippocampal sclerosis, although this was inconsistent across analyses. There was higher risk of Lewy bodies in substantia nigra and locus ceruleus with higher glucose levels in age band analyses. We did not find interactions between glucose levels, neuropathologic findings, and dementia. The mechanism by which glucose may impact dementia risk is still unknown.

1. Introduction

Diabetes has been found to be a risk factor for Alzheimer's disease and dementia (Gorelick et al., 2011; Kloppenborg et al., 2008). Recently, we reported an association between glucose levels and dementia risk, even among people with no history of diabetes treatment (Crane et al., 2013). The mechanisms by which elevated glucose levels may lead to increased dementia risk are not known.

Given this scientific uncertainty, we sought to determine whether there were associations between glucose levels and neuropathologic outcomes evaluated at the time of autopsy among people with no history of treatment for diabetes. We specifically focused on neuropathologic findings that are in turn associated with dementia. Our *a priori* hypothesis was that higher glucose levels would be associated with higher levels of Alzheimer's disease–related pathology of neuritic plaques and neurofibrillary tangles. These elements are captured by Braak stage (Braak and Braak, 1991) for neurofibrillary tangles and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) grade for neuritic plaques (Mirra et al., 1991). Previous work has also found that Lewy bodies, microinfarcts, and macroscopic infarcts including lacunar infarcts are associated with dementia (Sonnen et al., 2007), so we also evaluated associations between glucose levels and those neuropathologic outcomes, as well as amyloid angiopathy.

Glucose levels may directly lead to higher levels of any particular neuropathologic finding and thus to increased dementia risk. Alternatively, elevated glucose levels may impact dementia risk by altering cognitive resilience such that the burden of neurodegenerative changes one could tolerate before manifesting dementia is reduced. To address this, we used interaction models to explore whether glucose levels may alter thresholds of dementia risk for each neuropathologic finding. We therefore evaluated both

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whether there were associations between glucose levels and risk of dementia-related neuropathologic outcomes evaluated at death and whether glucose levels modified the relationship between these neuropathologic outcomes and risk of expressing the clinical manifestation of dementia.

In our prior analysis of the association between glucose levels and dementia risk, we considered glucose levels over the 5 years before dementia onset. For the current analyses, we identified 2 time periods of interest. Our *a priori* primary approach was based on biological considerations, and considered the period before death. These models in essence considered average glucose levels over the last several years of life as the exposure of interest.

Our *a priori* biological models may provide insight into disease etiology but would be difficult to use to make clinical decisions because we would have no way of knowing if a particular person was within the last few years of life. These considerations led us to a second, exploratory approach, which was to consider age bands late in life as our exposure time axis. Thus, models for these secondary analyses considered average glucose levels over specific ages of life as the exposure of interest.

The present report thus follows up our finding of an association between higher glucose levels and increased dementia risk among people with no history of treatment for diabetes (Crane et al., 2013) by exploring associations between glucose levels over several different time windows and neuropathologic findings at autopsy. Our overarching goal was to help elucidate mechanisms by which higher glucose levels in late life could contribute to dementia risk.

2. Methods

2.1. Study description

Our analyses used autopsied participants with no history of diabetes treatment from Adult Changes in Thought (ACT), a population-based prospective cohort study examining risk factors for dementia. The study is described in detail elsewhere (Crane et al., 2013; Kukull et al., 2002; Larson et al., 2006). Briefly, ACT participants are community-dwelling members of Group Health (GH), an integrated health care delivery system in the Pacific Northwest of the United States. Participants were required to be aged 65 or older and not demented at study enrollment; then they were followed with biennial interviews for continued demographic and risk factor ascertainment and cognitive screening evaluations with the Cognitive Abilities Screening Instrument, for which scores range from 0 to 100 and higher scores indicate better functioning (Teng et al., 1994). The Cognitive Abilities Screening Instrument assesses attention, concentration, orientation, memory, language, visual construction, verbal fluency, and judgment. Participants with scores of 85 or less underwent further clinical and psychometric evaluation, including a battery of neuropsychological tests. The dementia psychometric battery includes clock drawing (Spreen and Strauss, 1991), verbal fluency (Morris et al., 1989), Mattis Dementia Rating Scale (Mattis, 1988), Boston naming (Morris et al., 1989), verbal-paired associations and recall, logical memory and recall (Wechsler, 1987), Word List Memory (Morris et al., 1989), Constructional Praxis and recall (Morris et al., 1989), Trails A and B (Reitan and Wolfson, 1985), and Information and Comprehension subtest items (Wechsler, 1987). The results of these evaluations and laboratory testing and imaging records were then reviewed in a consensus conference. Diagnoses of dementia (American Psychiatric Association. Task Force on DSM-IV, 1994) and of probable or possible Alzheimer's disease (McKhann, 1984) were made on the basis of research criteria. Dementia-free participants continued with scheduled follow–up visits.

As participants were members of GH, information from electronic administrative databases—including laboratory measures, pharmacy dispensings, and diagnosis codes resulting from clinical encounters—could be linked to participants to augment data collected at ACT study visits. In addition, participants who died and had consented to brain autopsy underwent a complete historical medical record review to determine even more extensive comorbid history. All procedures were approved by the institutional review boards of GH and the University of Washington, and participants gave written informed consent.

2.2. Glucose characterization and modeling

GH pharmacy records were used to identify autopsied participants from ACT, who never appeared to have been using medications for treatment of diabetes. Among these participants, we ascertained measures of random and fasting glucose and glycated hemoglobin (HbA_{1c} or total glycated hemoglobin), taken as part of regular clinical care, through linkage with the GH computerized laboratory databases, as well from a complete historical medical record review. As in our prior glucose work within ACT (Crane et al., 2013), total glycated hemoglobin was converted to HbA1c using the formula (HbA1c $= 0.6 \times$ [glycated hemoglobin] $+ 1.7$), and HbA1c was transformed to daily average glucose using the formula (avg $= 28.7$ [HbA1c] $- 46.7$) (Nathan et al., 2008). Then, as in the prior analysis of glucose levels and dementia risk, we combined individual random and fasting glucose measures and daily average glucose using a hierarchical Bayesian framework (Carlin and Louis, 2000) to compute an estimated average glucose level for each 5-year period of each autopsied participant's life, covering time as recently as the 5 years before death and all the way back to the first availability of glucose/HbA1c measures for the individual. Computerized clinical laboratory data were available from 1988 onward; clinical laboratory data from medical records extended back as far as the 1940s for some individuals. Our prior report on clinical dementia outcomes was limited to the period from 1988 onward (Crane et al., 2013).

2.3. Neuropathology evaluation

Neuropathology workup for ACT has been reported elsewhere; we quote here from 2 studies (Li et al., 2007; Sonnen et al., 2007). Neuropathologic examinations were performed in the University of Washington Division of Neuropathology and the University of Washington Alzheimer's Disease Research Center Neuropathology Core. All neuropathologic assessments were performed blind to clinical diagnosis and status of risk factors. Brains were immersion-fixed in formalin for at least 2 weeks before dissection. After fixation, all brains were evaluated (wholly and after coronal sectioning) for any gross lesions, including the extent of atherosclerosis ("mild" when restricted to branch points in the circle of Willis; "moderate" when also in other regions at the base of the brain; and "severe" when present on the convexity of cerebrum) and the number of gross (macroscopic) infarcts including lacunar infarcts. We limited our evaluation to remote (estimated >1-year old) macroscopic infarcts, as acute and subacute infarcts were thought unlikely to have contributed to longstanding cognitive decline. Tissue sections were dissected from middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, anterior cingulate gyrus, primary visual cortex, basal ganglia at the level of the anterior commissure, thalamus, hippocampus at the level of the uncus, amygdala, midbrain including substantia nigra, pons at the level of the locus ceruleus, medulla, cerebellar hemisphere, and pituitary gland. These tissue sections were processed