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W241 Summer 21, Essay 1: Analysis of a Causal Claim

Association between Age at Diabetes Onset and Subsequent Risk of Dementia

Alzheimer's and diabetes (especially Type 2 diabetes, or "adult-onset diabetes") are two highly-studied illnesses that plague American medical professionals, and it appears that a link has been discovered between the two. An article from the New York Times, written by Nicholas Bakalar, summarizes the findings of a JAMA study published in late April 2021 and echoes the study's conclusion: "the younger the age at which diabetes is diagnosed, the greater the risk" (Bakalar, 2021) for dementia later in life. Specifically, for every five years that diabetes was diagnosed earlier, the individual had a 24% increased risk for dementia than those of the same age without a diabetes diagnosis.

The implications of such a statement are astounding. Alzheimer's, a form of dementia, is the fifth-most common cause of death among adults aged 65 and above, and currently has no cure nor therapy to alleviate the disease's impact (CDC, 2021). Additionally, about 9% of the US population has Type 2 diabetes and it continues to surface in younger and younger individuals (CDC, 2021). If early-onset of Type 2 diabetes truly leads to higher risk for Alzheimer's or other forms of dementia, then more and more Americans will find themselves diagnosed with this terminal illness. Conversely, these study results offer the hope that if the effects of Type 2 diabetes can be reversed or postponed with healthier habits and regimented diet, we may see a reduction in the risk of dementia.

The data that led to this conclusion was collected in an observational study by British researchers over a period of about 32 years, from 1988 to 2019. They tracked 10,095 men and women who were between 35 to 55 years old and free of diabetes or dementia through their later adult years, performing clinical examinations every 4-5 years and recording any changes in blood glucose levels or diagnosed cases of Type 2 diabetes. To determine whether study participants eventually demonstrated dementia (substantial cognitive impairment), researchers leveraged data linked to electronic health records from the British government. Other factors that could've contributed to dementia such as sociodemographic factors (sex, education, etc.), health behaviors (smoking, diet, physical activity, etc.), and health-related variables (e.g. heart conditions) were controlled for in this study, so while the study was observational, the researchers believe the result is significant.

However, it is dangerous to conclude causality from such an observational study. The information was collected over time and in 4 or 5-year intervals, during which many things could have changed within the participants' lives, such as their diet, lifestyle, and occupation. The study assumes that the participants would maintain the health behaviors recorded at the beginning of the study over time, but that is likely untrue. Any dramatic change to lifestyle could increase the participants' likelihood to develop dementia, and omitting these features from study analysis would result in an overestimate of the impact of diabetes onset on dementia. And for the participants that were diagnosed with diabetes during the study, no additional analysis was performed to account for the impact of that diagnosis on lifestyle, which may also have impacted

the development of dementia (or lack thereof) later in life. A diabetes diagnosis could encourage an individual to live a healthier lifestyle which would in turn lower the risk of dementia, and failure to incorporate this factor into the study covariates may underestimate the impact that an early diagnosis of diabetes has on the risk of dementia. Alternatively, it's possible that the mental strain of a diagnosis such as Type 2 diabetes would impact brain activity and actually be the defining factor for increased risk of dementia later in life, and if this is the case, the impact of the diabetes diagnosis would be overestimated in the study results.

Family history and genetics is another confounding variable that may impact the causal effect purported in this study. The researchers did record participants' FINDRISC (Finnish Diabetes Risk Score), which quantifies diabetes risk based on a number of factors including family history, but did not include it as a covariate in their analysis. Given how much we have to learn about the human body and genetics, if many of the individuals selected for this study had genetic predispositions for diabetes and/or dementia, the effect of diabetes on risk of dementia could've been overestimated due to omitted variable bias. By only including the 15 covariates in their analysis, the researchers assume that no other factors are crucial to development of dementia, and that any increased risk of dementia are attributed to the early onset of diabetes. But this is a difficult claim as we still have more to understand regarding dementia.

More uncertainty arises from the direction of the causal pathway between diabetes and dementia (if one exists). It is possible that individuals with a high risk for dementia are actually more prone to developing diabetes early in life, proposing the possibility that dementia may lead to early-onset diabetes, instead of the opposite. The researchers assume that health outcomes earlier in life will impact outcomes later in life, but it is also possible that an outcome that only manifests late in life will cause other negative health outcomes to manifest early on.

The ideal experiment to truly quantify the impact of age at diabetes onset on the subsequent risk of dementia would control for various factors this observational study was unable to capture. The experiment would require a sample of participants who all have the same likelihood of developing dementia later in life, and we would randomly separate those individuals into a control and test group. The treatment would be early-onset diabetes, defined as a diagnosis of Type 2 diabetes before the age of 45, and would be "administered" to all individuals (perhaps in the form of a drug) in the test group but withheld from all individuals in the control group. A strict regimen would be created for participants' diets and lifestyles, defining specific foods, activities, and the quantities of those, set for the next 20 years (or until they develop dementia). Then we would observe which experiment subjects develop dementia and analyze the results.

Such an experiment would be unfeasible (and very unethical), so a more likely path would involve randomly selecting individuals who were diagnosed with diabetes at a younger age and comparing their instances of dementia with a group of randomly-selected individuals who did not develop Type 2 diabetes. Their diets and physical activity should be defined by experiment researchers and progress towards dementia monitored. Only if these conditions are met can we infer a causal relationship between the age at which diabetes is diagnosed and the likelihood of developing dementia.

Appendix

Claudio Barbiellini Amidei, MD, et. all. *Association between Age at Diabetes Onset and Subsequent Risk of Dementia*. Journal of the American Medical Association. Accessed 08 May 2021. <https://jamanetwork.com/journals/jama/article-abstract/2779197> .

Bakalar, Nicholas. *Earlier Diabetes Onset Could Raise Dementia Risk*. The New York Times. Accessed 08 May 2021. <https://www.nytimes.com/2021/05/03/well/mind/diabetes-dementia-Alzheimers.html> .

Centers for Disease Control and Prevention (CDC). *Type 2 Diabetes*. US Department of Health & Human Services. Accessed 08 May 2021. <https://www.cdc.gov/diabetes/basics/type2.html> .

Centers for Disease Control and Prevention (CDC). *Alzheimer's Disease*. US Department of Health & Human Services. Accessed 08 May 2021. <https://www.cdc.gov/dotw/alzheimers/index.html#:~:text=Alzheimer's%20disease%20is%20the%20most,of%20death%20for%20all%20adults>.