Published in final edited form as:

N Engl J Med. 2016 July 07; 375(1): 93–94. doi:10.1056/NEJMc1604823.

Response by Satizabal et al. to Letter Regarding Article, “Incidence of Dementia over Three Decades in the Framingham Heart Study”

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THE AUTHOR’S REPLY:

We concur with Binder and Schumacher about the potential for bias because of the onset of dementia occurring between a participant’s last examination by Framingham Heart Study investigators and death. However, we review all medical records up to the date of death for all participants. If this review raises any concern that the participant might have had cognitive decline before death, we gather relevant additional data, which may include semi structured interviews with surviving family members, and conduct a full dementia review to assign a final cognitive status at the time of death. In our sample of 9015 observation periods for 5205 participants, 719 observation periods had censoring of data with the comment “dead and probably dementia-free,” since the medical-record review and family interview after death did not raise any concern about possible dementia. These 719 observation periods were distributed across all four epochs of the study, with 141 in the first epoch, 176 in the second epoch, 251 in the third epoch, and 151 in the fourth epoch. In a post hoc analysis in which data for these participants were censored at the last time they were actually seen and declared to be dementia-free (rather than at the time of death), the results remained essentially unchanged (Table 1).

In response to the question by Hinterberger *et al.*: we performed a post hoc analysis of trends for participants who were categorized as having “pure” Alzheimer’s disease rather than “mixed” Alzheimer’s disease. (Definitions of the two conditions and the results of the analysis are also provided in Table 1). The findings were similar in the two subgroups, with similar effect sizes.

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Disclosures: None

Since publication of their article, the authors report no further potential conflict of interest.

Table 1.

Risk of Dementia in the Framingham Heart Study over Time in Two Post Hoc Subgroups.*

Variable	Risk of Dementia				P Value for Trend
	Epoch 1	Epoch 2	Epoch 3	Epoch 4	
	<i>hazard ratio (95% CI)</i>				Trend
Data censored at death vs. last medical visit					
Censored at death in original study	1.00	0.78 (0.59–1.04)	0.62 (0.47–0.83)	0.56 (0.41–0.77)	0.80 (0.72–0.90)
Censored at last medical visit in post hoc subgroup analysis	1.00	0.80 (0.60–1.06)	0.63 (0.48–0.84)	0.58 (0.43–0.79)	0.81 (0.73–0.91)
Data for “mixed” Alzheimer’s disease vs. “pure” Alzheimer’s disease [†]					
Mixed Alzheimer’s disease in original study	1.00	1.00 (0.70–1.43)	0.88 (0.62–1.25)	0.70 (0.48–1.03)	0.88 (0.77–1.00)
Pure Alzheimer’s disease in post hoc subgroup analysis	1.00	0.86 (0.58–1.28)	0.84 (0.58–1.22)	0.67 (0.45–1.02)	0.87 (0.76–1.01)

* Hazard ratios were adjusted for age and sex in each 5-year epoch, as compared with the first epoch (reference group).

[†] Pure Alzheimer’s disease was defined as “definite or probable” Alzheimer’s disease, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRD), with no additional cause of dementia and “no possible” vascular dementia, according to the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) or the criteria of the Alzheimer’s Disease Diagnostic and Treatment Centers (ADTTC). Mixed Alzheimer’s disease was defined as pure Alzheimer’s disease plus “possible” Alzheimer’s disease, according to the criteria of NINCDS–ADRD, or “possible” vascular dementia, according to the criteria of NINDS–AIREN or ADTTC.