

Dear editor

Thank you for inviting us to respond to Wilkinson et al's letters about our recent paper on in-hospital diagnosis of dementia.

We agree with Kivimäki and Singh-Manoux's caveats about population attributable fraction (PAF), and state this explicitly in the commission "the PAF model assumes a causal association between a risk factor and dementia, and a causative link is required for interventions to lead to ... reductions in the incidence of dementia. With regard to causality, the most convincing evidence would be from randomised controlled trials (RCTs) in humans. These trials are not possible for many proposed dementia risk factors, such as education, but we know that falling age-specific incidence is associated with more education"<sup>1</sup>.

Apart from high quality observational evidence, we showed that, for example, peripheral hearing loss fits causality criteria<sup>2</sup>. In animals, deafness precedes changes in brain structure, volume and network<sup>1</sup>. Kivimäki and Singh-Manoux think hearing loss may be caused by preclinical neurodegeneration. This is unlikely as electrophysiological and post-mortem studies have not found evidence that Alzheimer's disease affects cochlear systems<sup>3</sup>. We do not know if the deaf community has higher rates of dementia, because we lack evidence on long term cognitive outcomes<sup>4</sup> but the deaf community have developed sign language as an alternative to spoken communication, so do not lose access to language as those with adult onset deafness do. Their rate of dementia, therefore, does not relate to whether reduction of acquired hearing loss might reduce dementia rates.

We also discussed reverse causality<sup>1</sup> but are unconvinced it is proved for depression. We cite Singh-Manoux's paper on this<sup>5</sup> in our commission as well as contradictory findings over 24 years' follow-up showing elevated dementia risk with recurrent episodes<sup>6</sup>. Depression may be part of a dementia prodrome but we do not know it is only that.

Similarly, Kivimäki and Singh-Manoux discuss whether dementia causes social isolation rather than social isolation causing dementia. Our recent joint paper, which meta-analysed all observational studies on dementia risk according to marital status, found that marriage, which may be the best way of reducing isolation, is associated with lower risk of dementia<sup>7</sup>.

We write in the commission, as Kivimäki and Singh-Manoux say, that "physical activity trials provide no evidence on dementia protection" but the studies they cited are in people who have mild cognitive impairment or dementia. If physical activity is protective it may take longer than the course of a trial to find out.

Yours sincerely

Andrew Sommerlad, Gayan Perera, Archana Singh-Manoux, Glyn Lewis, Robert Stewart, Gill Livingston

1. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; **390**(10113): 2673-734.

2. Hill A B. The environment and disease: association or causation? *Proc R Soc Med* 1965; **58**: 295-300.

3. Irimajiri R, Golob EJ, Starr A. Auditory brain-stem, middle- and long-latency evoked potentials in mild cognitive impairment. *Clin Neurophysiol* 2005; **116**(8): 1918-29.
4. Fellingner J, Holzinger D, Pollard R. Mental health of deaf people. *Lancet* 2012; **379**(9820): 1037-44.
5. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia A 28-Year Follow-up Study. *Jama Psychiatry* 2017; **74**(7): 712-8.
6. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology* 2010; **75**(1): 06-34.
7. Sommerlad A, Rieger J, Singh-Manoux A, Lewis G, Livingston G. Marriage and risk of dementia: systematic review and meta-analysis of observational studies. *J Neurol Neurosurg Psychiatry* 2017.