Research Open

Journal of Clinical Research and Medicine
Volume 8 Issue 2

Short Article

# With Normal Cognition at Age 60, is Future Alzheimer's Dementia Predictable?

**Jeffrey Fessel***

Department of Medicine, University of California, 2069 Filbert Street, San Francisco, CA 94123, USA

***Corresponding author:*** Jeffrey Fessel, Department of Medicine, University of California, 2069 Filbert Street, San Francisco, CA 94123, USA

**Received:** June 04, 2025; **Accepted:** June 09, 2025; **Published:** June 10, 2025

## Abstract

Whether or not an individual aged 60 with normal cognition, might develop Alzheimer's dementia (AD) in the future, depends upon the number of risk factors for AD affecting that person. That number is ten or more, amongst which are six proteins whose presence or absence can be measured. Clinical elements include diabetes mellitus, having no first degree relative with AD, past history of head trauma, and nutritional factors. In addition, the currently used medications with anti-cholinergic activities, if not discontinued, may provide significant additional risk for AD. This article describes how all of the above-mentioned risk factors relate to the risk for AD.

## Introduction and Background

How may a person aged 60 know if he/she still has predisposition for future Alzheimer's dementia (AD), despite having normal cognition as shown by detailed neuropsychological testing? The response is that the predisposition is proportional to the number of risk factors for AD affecting that individual. Ten of those potential risk factors are described here, including Wnt, TGFβ, Smad proteins, Cdk, neuregulins, apoE4, diabetes mellitus, having no first degree relative with AD, past head trauma, and nutritional factors. Besides those ten, the currently used medications with anti-cholinergic activities are also potential risk factors for AD and, if not discontinued, may provide significant addition to the predisposition. The following describes how the above-mentioned risk factors relate to the predisposition for AD (Table 1).

### Wnt and AD

There is dysfunction of the Wnt signaling pathway in AD [1], and Wnt/β-catenin dysfunction results in Aβ production and aggregation [2]. Further, down-regulation of the Wnt/β-catenin pathway leads to oxidative stress and neuronal cell death [3].

**Table 1:** Risk factors related to the predisposition for AD.

| Risk factor for AD | Confirmed by a Study? |
|---|---|
| Cardiovascular disease. | Conflictual reports. |
| Adherence to Mediterranean diet. | Conflictual reports. |
| Prior head trauma. | Yes but uncertain because studies used current AD patients. |
| Diabetes. | Yes. RR 1.8 with DM alone, 5.5 with DM + apoE4. |
| ApoE4 | Yes |
| Wnt | No |
| TGFβ | No |
| Smad proteins | No |
| Cdk protein. | No |
| Neuregulin | No |

### TGF-β and AD

In AD, the level of FAMC that is a key molecule in the formation of TGF-β, is reduced by ~30–50% [4,5]; that is detrimental because TGF-β protects neurons against neurotoxicity caused by Aβ [6]. Although TGF-beta 1 and TGF-beta 3 were not selectively altered in any AD subtypes, selective induction of TGF-beta 2 did occur in both late onset AD and Familial AD [7].

### Smad Proteins and AD

TGF-β acts by signaling through the Smad pathway. Whereas Snad acts from a nuclear localization, in AD it is predominantly cytoplasmic, so its action is defective [8].

### Cdk and AD

Cyclin-dependent kinase 5 (Cdk5), a serine/threonine protein kinase, has multiple and confusingly discrepant cellular activities; >30 substrates for Cdk5 have been found in different cellular pathways [9], and these may promote either cell toxicity or cell survival. It contributes to the occurrence of AD because it is implicated in the generation of Aβ peptides and it induces hyperphosphorylation and aggregation of tau10. Findings from AD brain samples also showed an elevated Cdk5 activity [9,11], that was promoted by Aβ12. Cdk5 promotes neuronal survival by regulating Akt activity via the neuregulin/phosphoinositol-3-kinase (PI-3-kinase) signaling pathway. Thus, brain extracts of Cdk5-/-mice had lower PI-3-kinase activity and phosphorylation of Akt compared with wild type mice. [10]; and although treatment of rat hippocampal cells in culture with Aβ resulted in a significant increase of the Cdk5 enzymatic activity, the neurotoxicity of Aβ was diminished by inhibition of Cdk5[13].

### Neuregulins and AD

Recombinant neuregulin prevented the neurotoxicity caused by oxidative stress [14]; and because neuregulin level was reduced in the hippocampus of AD patients, its absence contributes to the occurrence of dementia [15].

### ApoE4 and AD

Many genes and their associated mRNA and proteins are risk factors for late-onset AD; among the many relevant genes shown by a multi-center study, APOE4 had huge significance ($P = 3.3 \times 10{-}96$) [16]. Its beneficial action in AD involves Aβ aggregation and clearance, tau phosphorylation, aggregation and clearance, lipid metabolism, inflammation, altered neuronal repair, and synaptic plasticity [17].

### Diabetes Mellitus and AD

The relative risk (RR) for AD with diabetes alone was 1.8 but with both diabetes and ApoE4 was 5.5 [18]. After adjustment for several confounders, the same report shows the increased effect of the dual combination beyond that of its components, in which the RR for AD without cerebrovascular disease was 1.0 for diabetes alone, 2.0 for ApoE4 alone, and 4.2 for the diabetes/ApoE4 combination.

### Nutrition and AD

Reports are conflictual regarding the effect of nutrition upon the possibility for future AD. The Mediterranean diet is one that is rich in vegetables, fruit, cereals, olive oil, red wine (two glasses daily), white meat, and sea food, but little red meat. Although several other studies gave negative results with respect to adherence to that diet and the occurrence of either cognitive impairment or AD, a large study involving 2,258 community-based non-demented individuals in New York evaluated them every 1.5 years and produced positive results [19]. There were 262 incident AD cases during 4 years of follow-up. After adjusting for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical comorbidity index, and body mass index, higher adherence to the Mediterranean diet was associated with a substantially lower risk for AD (hazard ratio, 0.91; $p = 0.015$): as compared with subjects in the lowest tertile for adherence to the diet, those at the highest tertile had a hazard ratio of 0.60 (95% confidence interval, 0.42–0.87) for subsequent AD (P for trend = 0.007).

### Cardiovascular Disease and AD

Cardiovascular diseases, such as stroke, atrial fibrillation, coronary heart disease, and heart failure are very common in elderly individuals and have regularly been linked to AD, but this association might be due to shared risk factors between cardiovascular diseases and AD, although there might also be a direct causal association as cardiac disease causes hypoperfusion and microemboli [20]. The shared and modifiable risk factors include smoking, lack of physical exercise, hyperlipidemia, and hypertension [21]. Moreover, amyloid-beta (Aβ) deposits, present in brain parenchyma of patients with AD, are also seen in human atherosclerotic plaques or cardiac tissues of patients with heart failure, suggesting the involvement of Aβ in both AD and cardiovascular disease [22].

### Drugs with Anti-cholinergic Activity

Those drugs are numerous and are listed by the American Geriatrics Society [23].

### First Degree Relatives with AD, as a Risk Factor

In a Swedish study of the risk factors for late-onset AD, involving 98 cases and 216 controls, the Relative Risk (RR) was 3.2 (95% CI, 1.8-5.7) if at least one first-degree relative had dementia [24].

### Head Trauma and AD

Prior head injury was assessed in 78 patients with AD and 124 controls matched for age, sex, and race [25,26]. A history of head injury with loss of consciousness was reported in 25.6% of patients and 5.3% and 14.6% of hospital and neighborhood controls, respectively; for patients and hospital controls the odds ratio was 4.50 ($P < 0.01$). Interestingly, the ranges of times of occurrence of head injuries were similar in patients and controls, spanning several decades.

## Discussion

Should the appraisal of prediction from each contributing factor to future AD be multiplicative or additive? In fact, for the 60 years' old person who has no current cognitve impairment, the probability of future AD would be very low if there were no predisposing elements; and although the probability increases with the escalating number of those elements that are present, that probability remains intuitive because there are no empirical observations that provide numerical values. Regarding the risk of future AD for that individual, the presence or absence of the six proteins that are risk factors may be ascertained by laboratory testing so, if present, the best method used for their appraisal of prediction should be additive because multiplicative would exaggerate the prediction.

## References


1. Kostes WW, Brafman DA (2023) The Multifaceted Role of WNT Signaling in Alzheimer's Disease Onset and Age-Related Progression. *Cells* 12: 1204. [crossref]
2. Inestrosa NC, Tapia-Rojas C, Cerpa W, Cisternas P, Zolezzi JM (2021) In Pharmacology of the WNT Signaling System 357-382.
3. Vallée A, Lecarpentier Y, Guillevin R, Vallée J-N (2018) Reprogramming energetic metabolism in Alzheimer's disease. *Life Sci.* 193: 141-152.
4. Huang L, Jia J, Liu R (2013) Decreased serum levels of the angiogenic factors VEGF and TGF-β1 in Alzheimer's disease and amnestic mild cognitive impairment. *Neurosci. Lett* 550: 60-63. [crossref]
5. Mocali A, Cedrola S, Della Malva N, Bontempelli M, Mitidieri VA, et al. (2004) Increased plasma levels of soluble CD40, together with the decrease of TGFβ1, as possible differential markers of Alzheimer disease. *Exp. Gerontol* 39: 1555-1561. [crossref]
6. Chao CC, Hu S, Kravitz FH, Tsang M, Anderson WR, et al. (1994) Transforming growth factor-β protects human neurons against β-amyloid-induced injury. *Molecular and Chemical Neuropathology* 23: 159-178. [crossref]
7. Flanders K, Ren R, Lippa C (1998) Transforming growth factor-betas in neurodegenerative disease. *Prog. Neurobiol* 54: 71-85. [crossref]
8. Lee H-g, Ueda M, Zhu X, Perry G, Smith M (2006) Ectopic expression of phospho-Smad2 in Alzheimer's disease: Uncoupling of the transforming growth factor-β pathway? *J. Neurosci. Res* 84: 1856-1861. [crossref]
9. Cortés N, Guzmán-Martínez L, Andrade V, González A, Maccioni RB (2019) CDK5: a unique CDK and its multiple roles in the nervous system. *Journal of Alzheimer's Disease* 68: 843-855. [crossref]

10. Li B-S, Ma W, Jaffe H, Zheng Y, Takahashi S, et al. (2003) Cyclin-dependent kinase-5 is involved in neuregulin-dependent activation of phosphatidylinositol 3-kinase and Akt activity mediating neuronal survival. *J. Biol. Chem* 278: 35702-35709. [crossref]

11. Shukla V, Skuntz S, Pant HC (2012) Deregulated Cdk5 activity is involved in inducing Alzheimer's disease. *Arch. Med. Res* 43: 655-662. [crossref]

12. Lee M-S, T sai L-H (2003) Cdk5: one of the links between senile plaques and neurofibrillary tangles? *Journal of Alzheimer's Disease* 5: 127-137. [crossref]

13. Alvarez A, Toro R, Cáceres A, Maccioni RB (1999) Inhibition of tau phosphorylating protein kinase cdk5 prevents β-amyloid-induced neuronal death. *FEBS Lett* 459: 421-426. [crossref]

14. Jiang Q, Chen S, Hu C, Huang P, Shen H, et al. (2016) Neuregulin-1 (Nrg1) signaling has a preventive role and is altered in the frontal cortex under the pathological conditions of Alzheimer's disease. *Mol. Med. Report* 14: 2614-2624. [crossref]

15. Kim Y-J, Yoo JY, Kim OS, Kim HB, Ryu J, et al. (2018) Neuregulin 1 regulates amyloid precursor protein cell surface expression and non-amyloidogenic processing. *J. Pharmacol. Sci* 137: 146-153. [crossref]

16. Naj AC, Jun G, Reitz C, Kunkle BW, Perry W, et al. (2014) Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. *JAMA neurology* 71: 1394-1404. [crossref]

17. Verghese PB, Castellano JM, Holtzman DM (2011) Apolipoprotein E in Alzheimer's disease and other neurological disorders. *The Lancet Neurology* 10: 241-252. [crossref]

18. Peila R, Rodriguez B, Launer L (2002) Honolulu-Asia Aging Study Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies. *Diabetes* 51: 1256-1262.

19. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA (2006) Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* 59: 912-921. [crossref]

20. de Bruijn RFAG, Ikram MA (2014) Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* 12: 1-9. [crossref]

21. Saeed A, Lopez O, Cohen A, Reis SE (2023) Cardiovascular disease and Alzheimer's disease: the heart–brain axis. *Journal of the American Heart Association* 12: e030780. [crossref]

22. Aivalioti E, et al. (2025) Amyloid-beta metabolism in age-related neurocardiovascular diseases. *Eur. Heart J* 46: 250-272.

23. Panel AGSBCUE (2023) American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc* (2023) 71: 2052-2081. [crossref]

24. Fratiglioni L, Ahlbom A, Viitanen M, Winblad B (1993) Risk factors for late-onset Alzheimer's disease: A population-based, case-control study. *Ann. Neurol* 33: 258-266. [crossref]

25. Mortimer J, French L, Hutton J, Schuman L (1985) Head injury as a risk factor for Alzheimer's disease. *Neurology* 35: 264-267. [crossref]

26. Liu Y, Wu Y, Cai J, Zhou H (2010) Additive–multiplicative rates model for recurrent events. *Lifetime Data Anal* 16: 353-373. [crossref]


**Citation:**

Fessel J (2025) With Normal Cognition at Age 60, is Future Alzheimer's Dementia Predictable? *J Clin Res Med* Volume 8(2): 1-3.