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The Gravity of Weight

## Alzheimer's Disease: The Inevitable Presence of Absence

Does metformin have any role in Alzheimer's disease?

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### KEY POINTS

- Alzheimer's, a progressive neurodegenerative disease, affects memory, cognition, personality, and behavior in over 24 million people worldwide.
- Those with Type 2 diabetes are at a higher risk of developing Alzheimer's, which is sometimes referred to as Type 3 diabetes.
- To date, there is no treatment, but researchers are repurposing medications like metformin with the hope of stopping the inevitable course.



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"To a person who loves, is not absence the most certain...the most durable, the most indestructible...of presences"?(Proust, *Pleasure and Days*, 1896.)

Nowhere does Proust's quotation resonate more than in Amy Bloom's description of her architect husband's cognitive decline in the extraordinarily moving, *In Love: A Memoir of Love and Loss* (2022). Bloom writes, "Sometimes now with Brian, I am worse than alone. I'm gone from his interior landscape."

The book poignantly chronicles her husband's subsequent decision to opt for assisted suicide after a diagnosis of Alzheimer's disease (AD).

AD, an “age-dependent progressive neurodegenerative disease” (Austad et al, 2022), is the most common cause of dementia. It affects 24 million people worldwide (Khezri et al, 2022), with two-thirds of cases in women, and is characterized by a decline in memory, cognition, as well as changes in behavior and personality (Kandimalla et al, 2017).

Researchers have studied Alzheimer’s disease, first identified more than a century ago (Sanati et al, 2022; Cipriani et al, 2011), for years.

We know about its pathology, namely the presence of beta-amyloid plaques and neurofibrillary tangles, as well as evidence of neuroinflammation and atrophy in the postmortem brains of those afflicted. We even know that these changes occur decades before the onset of measurable cognitive impairment (Liao et al, 2022).

But not all investigators agree on whether these processes are causative or merely correlated.

Says Bloom, “Nobody seems to know what they’re doing. There is literally no treatment. The most advanced Alzheimer’s research in the world says, ‘Eat (expletive) blueberries. Get enough (expletive) sleep.’”

Bloom is correct: To date, there is “no precise and effective treatment strategy” to reverse the disease (Sanati et al). It is not for a lack of trying.



An old woman tearing at her hair by Netherlandish painter Quentin Matsys, 1525-30. Prado Museum, Madrid. Aging is the most prominent risk factor for developing Alzheimer's disease, which is far more common in women.

Source: Fine Art Images/Bridgeman Images, used with permission

Some researchers, such as Richard Isaacson, a neurologist and the director of the Alzheimer's Prevention Clinic at New York-Presbyterian Hospital (Weill Cornell Medicine), believe a comprehensive evaluation and *very early* intervention, including diet and lifestyle changes, may hold the key to interfering with Alzheimer's inevitably progression.



Alois Alzheimer, 1864-1915, a German neuropathologist, credited with describing the clinical and pathological findings now associated with his name, in 1906.

Alzheimer's patient had early-onset dementia at age 51 and died at age 55.

Source: Colport/Alamy Stock Photo, used with permission

While these changes may hold promise for some, to date, no medication has yet proved clinically efficacious. In their search, though, investigators have turned to *repurpose* medications already on the market (Kulkarni et al, 2022).

The drug metformin, one of the most commonly prescribed medications worldwide as the first-line treatment for Type 2 diabetes, has shown potential in studies on aging and specifically for Alzheimer's disease (Kulkarni et al, 2022). Research, unfortunately, sometimes leads to contradictory findings.

In one preclinical rodent study, for example, metformin did not result in, as in previous research, any life-extension benefit or reductions in insulin or glu-

cose, leading Allison and colleagues to speculate that their choice of *rat strain* may have contributed to their disappointing results (Smith et al, 2010).

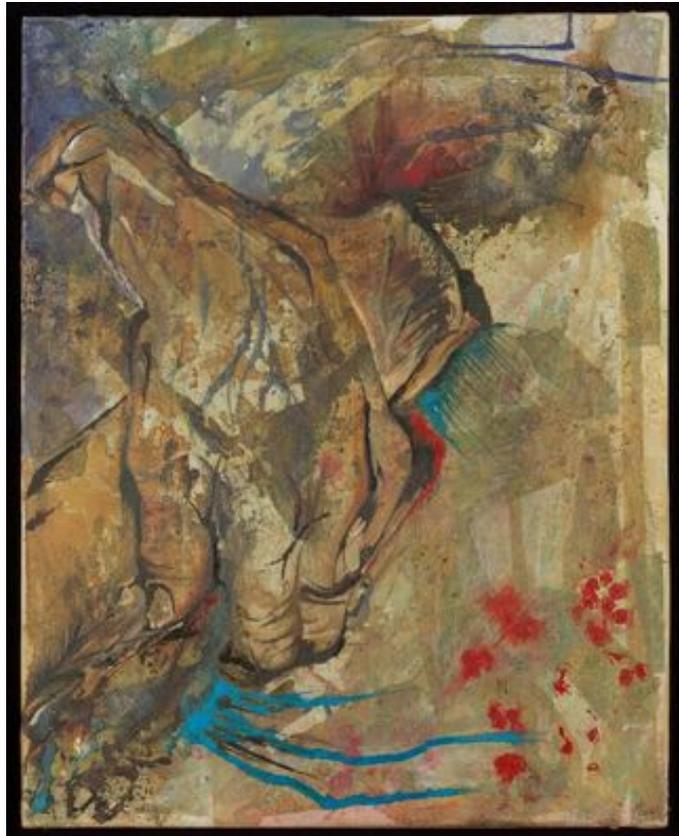
Further, though there is a substantial literature on the use of metformin for many different health outcomes, Ioannidis et al's "umbrella" review of over 425 different meta-analyses, including randomized controlled trials (RCTs) and observational reports, found that most studies were of "low or critically poor quality" and even "largely unre-

liable” (Li et al, 2021). These investigators found considerable heterogeneity among studies and most of the RCTs did not even provide information on the duration of follow-up or the dosage of metformin used. Potential conflicts of interest, as well, were often not clearly identified.

Why would investigators, though, even consider metformin in research on Alzheimer's disease?

The answer is that there is "convincing evidence" that AD "could be considered" a metabolic disorder and in some studies, 80% of subjects with AD have insulin resistance or Type 2 diabetes (Boccardi et al, 2019) and those with Type 2 have a higher risk of developing Alzheimer's (Meng et al, 2020; Austad et al).

There are even those who consider it not just a metabolic disease but *Type 3 diabetes* (Kandimalla et al, 2017; Liao et al; Top et al, 2022). There is "no definite conclusion" on the link between Alzheimer's and Type 2 diabetes but their "similar pathogenesis" has led to numerous studies that examine the effect of medications like metformin on AD (Meng et al).



"Mamamania: An artistic interpretation of Alzheimer's disease," based on the artist's grandmother, by Florence Winterflood. No date was given.

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*TAME: Targeting Aging with METformin* is one such double-blind placebo-controlled study that is enrolling thousands of subjects. Its mission is to create “a paradigm” for evaluating pharmacological approaches to delay the diseases of aging, including Alzheimer's (Soukas et al, 2019; Kulkarni et al, 2022; Kulkarni et al, 2020), and to increase "healthspan" i.e., the number of years of living "relatively free from disease"

(Newman et al, 2016). Metformin is the drug of choice because of its excellent safety record and “emerging evidence” that it may “preserve cognitive function” (Barzilai et al, 2016).

There is some evidence that metformin may lower the risk of developing AD in patients with Type 2 diabetes (Liao et al). Further, metformin’s anti-inflammatory and antioxidant properties in AD, among other mechanisms, “represents a constructive reason,” for using it in these patients (Khezri et al).

Not all studies concur, often because of differences in the study population, dose, and length of exposure to metformin (Khezri et al), as well as subjects' APOE4 (a potential genetic marker for developing AD), carrier status (Ning et al, 2022; Wu et al, 2020).

One systematic review with meta-analysis (four controlled trials and 24 observational studies), including subjects with and without diabetes who took metformin, for example, could not confirm its beneficial effects either on improving cognition or on preventing AD, though the researchers acknowledge their findings are “not conclusive” (Malazy et al, 2022).

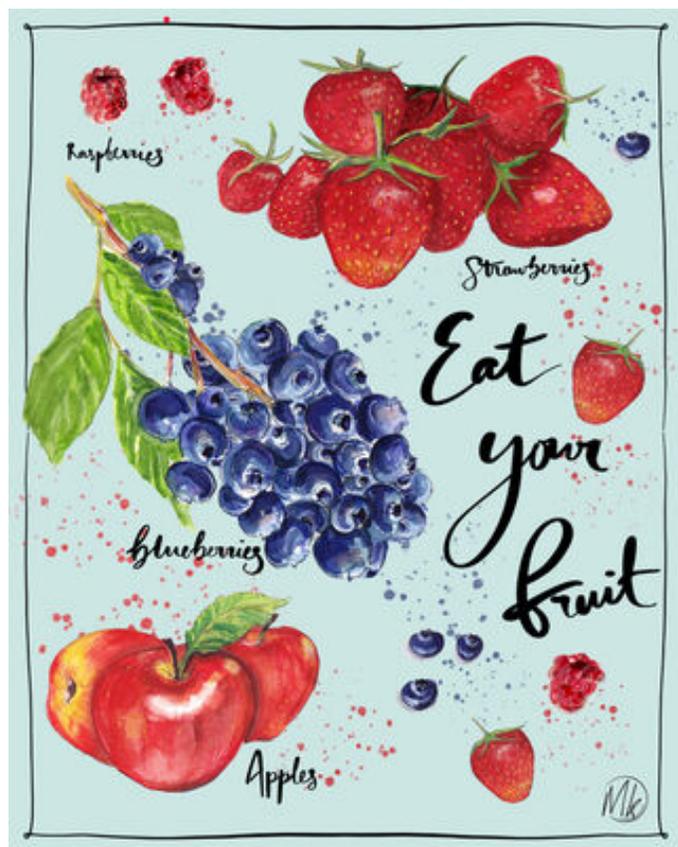
Some studies, as well, suggest that metformin may have benefits in cognitively normal people, especially if they don't have the APOE4 genetic marker, but once there is cognitive impairment from AD, "metformin might no longer be protective" (Wu et al).



"Erased self-portrait," by Philadelphia-born artist William Utermohlen, 1999, diagnosed with Alzheimer's disease. Private collection. See the Crutch et al reference for Utermohlen's history.

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"Overall," using metformin therapeutically for Alzheimer's remains "quite controversial" (Ning et al), and "ambiguous and conflicting" (Liao et al). As a result, many researchers urge caution and recommend an "individualized, precision approach" since there is no consensus about metformin's usefulness in the treatment of Alzheimer's (Soukas et al; Ning et al; Liao et al).



"Eat Your Fruit," by English artist Marianna Kulukundis, 2020. Private Collection.

Source: Photo credit: copyright Marianna Kulukundis, 2022/Bridgeman Images. Used with permission.

In that context, though, clinicians do seem to agree that we should all keep eating our (expletive) blueberries.

For a discussion of the early history of metformin, [see my previous post](#).

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