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Alzheimer's Disease: A Washing Machine on the Fritz

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Abstract

A mathematical model has been developed to numerically model the risk of developing Alzheimer's disease and Chronic Traumatic Encephalopathy (CTE) as a person ages. The model was programmed in Excel to provide a working prototype computer simulation model. The model provides estimates of the cumulative risk of developing Alzheimer's disease and CTE as age increases. A one-year step size was used. The model has two major parts: one predicts changes in slow-wave sleep as a person ages and the second component adjusts the flushing efficiency of waste products from the brain. The two components work together and interact to lower the flushing of waste components as age increases. The development of the model provides an overview of how the various factors work together that lead to the onset of Alzheimer's disease and the associated CTE. Calibration of the coefficients in the model is based on published data sets presented in the literature. Further research and refinement of calibration coefficients should be explored.

Keywords

Alzheimer's Disease, Sleep, Mathematical Modeling, Chronic Traumatic Encephalopathy CTE, Aging, Depression, Amyloid β, Tau

1. Introduction

Alzheimer's disease is a complex, progressive brain deterioration that results in memory loss and loss of mental function. It associates with the accumulation of protein fragments (amyloid β) that clump outside neurons and tau tangles that accumulate inside neurons [1]. Usually, amyloid β starts to accumulate first in the front center lobe of the brain that communicates with the hippocampus to convert short-term memory information to long-term memory [2]. As the disease progresses, both amyloid β and tau tangles increase [3] [4]. Both accumula-

tions are harmful to brain functions. Because the early development of amyloid β affects one of the components used in the conversion from short-term to long-term memory and memory consolidation, it is logical that one of the early symptoms of Alzheimer's disease is problems with memory.

Various causes have been suggested. Suggested causes include genetics, primarily the APOE4 allele but include other genes, inflammation, mental trauma including depression, physical trauma from head impacts, pressure waves, sleep issues, and lifestyle including exercise to name a few. Many other factors, including education and environmental pollution, also influence the rate of progression. Age provides the time for the various processes to operate leading to the deterioration of many parts of the brain. As the disease develops, brain structure changes, including the loss of brain volume [1] [5] [6] [7] [8] and the accumulation of amyloid β and tau tangles. As these changes occur, mental performance and memory, especially short-term memory deteriorates.

While many factors influence the rate of development, the root cause has not been identified. Certainly, many factors are involved in the development as a person ages. Some of these factors can be managed to slow the progression but need to be controlled early in the process to obtain maximum effect. Thus, a model to simulate and preview the risks associated with changes in the various contributing factors would be a useful tool.

Numerous studies have reported the APOE4 allele as the primary genetic risk factor [9]-[19]. Safinia *et al.* [19] report an estimate of 23 percent of the general population has one APOE4 allele. Corder *et al.* [20] studied familial and sporadic forms of Alzheimer's disease. They reported a dose relationship associated with the APOE4 allele. They reported an 8-fold increase in the risk of late-onset Alzheimer's disease for people with an APOE4 allele from each parent. Safinia *et al.* [19] suggest that having two APOE4 alleles leads to an 80 percent chance of developing Alzheimer's disease by age 75. Thus having an APOE4 allele is a major risk factor for developing Alzheimer's disease.

There is evidence that APOE4 disrupts lipid homeostasis in glial metabolism [9]. The glial cells are a major component of a healthy brain: shrinking during slow-wave sleep to flush away waste materials, such as amyloid β ([2] page 160) [21] [22] [23]. These glial cells can experience damage from impact sports, such as boxing and football [19]. Thus, there is evidence that both APOE4 alleles and impacts on the brain are risk factors for CTE discussed later in this paper.

Gofrit *et al.* [24] state that Alzheimer's disease has three major pathological features: amyloid β, neurofibrillary tangles, and sustained innate neuroinflammation. They suggest that inflammation is a major player in Alzheimer's disease pathogenesis. In another paper, Gofrit *et al.* [25] hypothesize that Bacillus Calmette-Guerin (BCG), a vaccine against tuberculosis, reduces inflammation in the brain and, thus, explains why people receiving the vaccine have a reduced risk of developing Alzheimer's disease. People treated for bladder cancer with BCG had a 4-fold reduction in risk of developing Alzheimer's disease compared

to people without treatment.

Our exposure to infections may contribute to our risk of developing inflammation and Alzheimer's disease [26]. Hussein [26] reviewed the history of how researchers have concluded that a connection exists between inflammation and Alzheimer's disease. He reported a 2.5-fold higher risk of developing Alzheimer's disease for people with antibodies associated with primary infection or reactivation.

There is compelling evidence that both APOE4 and infections contribute to an increased risk of developing Alzheimer's disease. Both, however, are processes that require time to develop.

Other factors that contribute to the risk of developing Alzheimer's disease are mental trauma including depression [15] [27]-[33], physical trauma from head impacts [19] [34] [35] [36] and pressure waves [37]. Byers, Yaffe [29] and Green *et al.* [15] have reported an approximately 2-fold increased risk for Alzheimer's disease in association with depression. Green *et al.* [15] reported a dose-effect based on the interval between the onset of depression and onset of Alzheimer's disease. Most likely, this time interval indicates the number of years associated with depression. Even if depression is treated, the increased risk for Alzheimer's disease may remain. Kessing *et al.* [38] noted that the odds for Alzheimer's disease are lowered by some of the older antidepressants.

Finally, there is a strong connection between the development of Alzheimer's disease and slow-wave sleep ([2] pages 157-163). This connection will be discussed later in this paper. Lifestyle, especially fitness through exercise is another variable [39] [40].

Age provides the time for the various processes to operate leading to the deterioration of many parts of the brain. As the disease develops, brain structure changes, including loss of brain volume [1] [5] [6] [7] [8] and the accumulation of amyloid β and tau tangles. As these changes occur, mental performance and memory, especially short-term memory deteriorates.

The process of development has numerous variables. No one thing, such as genetics or inflammation explains the full process. There obviously is a need for a model to explain the process.

Objective

Based on the many factors and often suggested causes, there is uncertainty about the system that controls the development of Alzheimer's disease. Walker [2] makes a strong argument that sleep interacting with the flushing of waste materials controls the development of Alzheimer's disease. On the other hand, Hussein [26] argues against the flushing hypothesis and suggests that infections are the cause. Could both be right to some degree? Needless to say, there is a need for a more complete mathematical model to describe the development of Alzheimer's disease.

The objective of this article is to present a mathematical model that offers a

possible explanation of how Alzheimer's disease develops and progresses with aging. Connections to the development of CTE are included.

2. Method

2.1. Model Development

The proposed Alzheimer's disease risk model is built on two major components or tasks:

(1) the expression of slow-wave sleep that controls the timing for engaging the glymphatic system to flush waste products from the brain, and
(2) the effect of genes and injury on the efficiency of the flushing system.

There is considerable evidence [2] [41] [42] that sleep, especially slow-wave sleep is an important factor in the development of Alzheimer's disease. Certain areas of the brain seem to be affected first. Early in the development of Alzheimer's disease, amyloid β starts to build up in the middle frontal lobe of the brain involved in controlling or staging slow-wave sleep. This area of the brain communicates with the hippocampus to convert short-term memory to long-term memory. The front lobe also is used in our executive function. Walker ([2] page 158) reports that the more amyloid deposits in the middle frontal lobe, the more impaired the deep-sleep or slow-wave sleep is in older individuals. Because amyloid β plaques are poisonous to neurons destroying the function of surrounding brain cells, the build-up of amyloid β in the middle frontal lobe accelerates the loss of slow-wave sleep compared to normal aging. It appears to be evidence of the beginning development of Alzheimer's disease.

Coupled with the switching on and off of slow-wave sleep is the turning on and off a 10 to 20 times increase in the flushing of waste products, such as amyloid β and tau tangle materials ([2] page 160) [12] [22] [23]. This increase in the effectiveness of the glymphatic system to literally flush away waste materials from the brain is critical to a healthy brain. Mestre *et al.* [21] report that "while there are several distinct neurodegenerative causes, cerebral small vessel disease (SVD) can be found in all forms". They suggest that glymphatic impairment plays an important role in SVD. This system of flushing (biological washing machine) can be compromised by the loss of slow-wave sleep or damage to the glial cells. Glial cells next to neurons in the brain can shrink by as much as 60 percent during slow-wave sleep providing space to flush toxins away from neurons into the cerebrospinal fluid to clean the metabolic refuse left by a day's neural activity ([2] page 161).

Sleep management and sleep quality have been linked to the buildup of amyloid β and tau in the spinal fluid of humans [41] [42]. Sleep disruption was found to increase amyloid β in the fluid bathing the brain and spinal cord. Poor-quality sleep over a few days was associated with higher levels of tau in the cerebrospinal fluid. The evidence is strong that for good brain health, we need quality sleep, especially slow-wave sleep.

The risk of developing Alzheimer's disease seems to be associated with the accumulation of amyloid β waste in the brain. Thus, the risk for developing Alzheimer's disease can be estimated by summing the waste contribution from birth to the desired age. The following equation (derived in **Appendix A**) estimates the non-flushed waste that accumulates after one night of sleep:

$$W_F = W_0 e^{-A_1 F_e S_{WF}} \quad (1)$$

where W_F = waste products remaining in the brain

W_0 = waste production

A_1 = calibration coefficient

F_e = flushing system efficiency

S_{WF} = time in slow-wave sleep during a night of sleep

Equation (1) expressed specifically for amyloid β is shown in Equation (2):

$$\beta = \beta_0 e^{-A_1 F_e S_{WF}} \quad (2)$$

where β = amyloid β remaining in the brain

β_0 = amyloid β production

Equation (1) expressed specifically for tau is shown in Equation (3):

$$\tau = \tau_0 e^{-A_1 F_e S_{WF}} \quad (3)$$

where τ = tau remaining in the brain

τ_0 = tau production

The risk of developing Alzheimer's disease seems to be associated with the accumulation of amyloid β waste. Thus, the risk for developing Alzheimer's disease can be estimated by summing the amyloid β waste remaining in the brain for each day of life divided by the minimum amount of amyloid β associated with symptoms of Alzheimer's disease:

$$R = \frac{1}{\beta_R}\left(1 - R_T\right)\sum_0^T \beta_0 e^{-A_1 F_e S_{WF}} \quad (4)$$

where β_R = a reference amount of amyloid β generally associated with the onset of Alzheimer's disease symptoms

R_T = accumulated risk through previous step calculation

T = total time (days for Equation (4); years for Equation (5))

The $(1 - R_T)$ component in the above equation limits the waste accumulation to a probability of developing Alzheimer's disease. Note that many of the variables in Equation (4) may vary daily as a function of other variables. For example, there is growing evidence [43] that genetics through APOE alleles affect the generation of amyloid β_0. Sleep amount and quality vary with individuals, management by individuals, and other variables, such as age and exercise.

Equation (4) estimates the risk of developing Alzheimer's disease associated with one day. Daily values are needed for each variable. Data input can be greatly reduced by multiplying the right side of Equation (4) by 365 days/year and using average daily values for a year as input:

$$R = \frac{365}{\beta_R}\left(1 - R_T\right)\sum_{0}^{T}\beta_0 e^{-A_1 F_e S_{WF}} \quad (5)$$

While this change is a practical step to estimate results for a general population, it removes the ability to estimate risk for an individual with highly variable sleep management. A process to estimate an average slow-wave sleep amount is presented in **Appendix B**.

Next, we can adjust the slow-wave sleep by multiplying the normal amount of slow-wave sleep by $(1 - R_T)$, where R_T represents the risk total up to the current age or year of calculation. It is logical that the buildup of amyloid β and tau tangles in the brain should reduce the various brain functions, such as slow-wave sleep and flushing efficiency. The $(1 - R_T)$ defines the F_e variable when no mechanical insults to the brain have occurred.

These equations and adjustments were programmed in Excel using a step size of one year using the R_T from the previous step to update the calculations for the current step. Data reported by the Alzheimer's Association [1] were used to calibrate and verify the model. The number of data points is limited. This report provides that 5.3 percent age 65 - 74, 13.8 percent age 75 - 84, and 34.6 percent age 85 and older have Alzheimer's disease. To compare to the calculated values, we need a specific age instead of a range. Ages for comparison were calculated as follows: (65 + 74)/2 = 69.5 and (75 + 84)/2 = 79.5. These ages were rounded up to the nearest whole number: 70 and 80 respectively. The number for 85 and older is more ambiguous. It certainly must be larger than 90 years. The question is how much more? The upper range certainly could be 100 or larger. On the other hand, only a small percentage of people live over 100 years. To deal with this extended range, it was assumed that a range of 15 years instead of 10 years was a reasonable estimate for ages 85 and older: (85 + 100)/2 = 92.5 years. This number was rounded up to the nearest whole number, 93. Based on the beginning boundary condition, a 0 risk was used for age 0 to obtain an additional data point. An $R^2 = 0.999$ was obtained comparing measured to predicted data for the four ages. With four data points, the significance or probability of being a random fit was $p < 0.001$. The values for A_1 (6.6) and β_0/β_R (0.000096 for Equation 4; 0.035 for Equation (5)) were determined from this process. The predicted curve for risk as a function of age from birth to 120 years of age and the measured data are shown in **Figure 1**. **Figure 1** also illustrates the trend and boundary conditions (0, upper limit ≤ 1.0) for risk. Note that the trend is highly nonlinear and cumulative over a lifespan.

Because of the uncertainty of the age to be used for 85 and older, the calibration was tested without the 93 years age prediction. The R^2 reduced to 0.998 ($p = 0.05$). Either result seems to verify the model to predict the risk of developing Alzheimer's disease for general conditions.

The predicted values also were compared to the cumulative risk of developing Alzheimer's disease provided by [18]. This data set contained 50 different ages. Without any changes in calibration, the predicted values matched these reported

values with an R^2 equal to 0.99, which was highly significant ($p < 0.001$). Results are shown in Figure 2. The slope of the linear portion in Figure 2 is approximately 0.034, essentially the same as the calibration value for β_0/β_R.

A mathematical model is no better than the data set used for calibration. It appears that the Alzheimer's Association either used the data from Lautenschlager *et al.* [18] or that they used independent data in agreement with the Lautenschlager data. The mathematical model developed at this point has the advantage that it includes theoretical boundary conditions of 0.0 at birth and 1.0 as a maximum probability value. It will be shown in the next section that Equation 5 as calibrated for Alzheimer's disease can also estimate the risk of developing

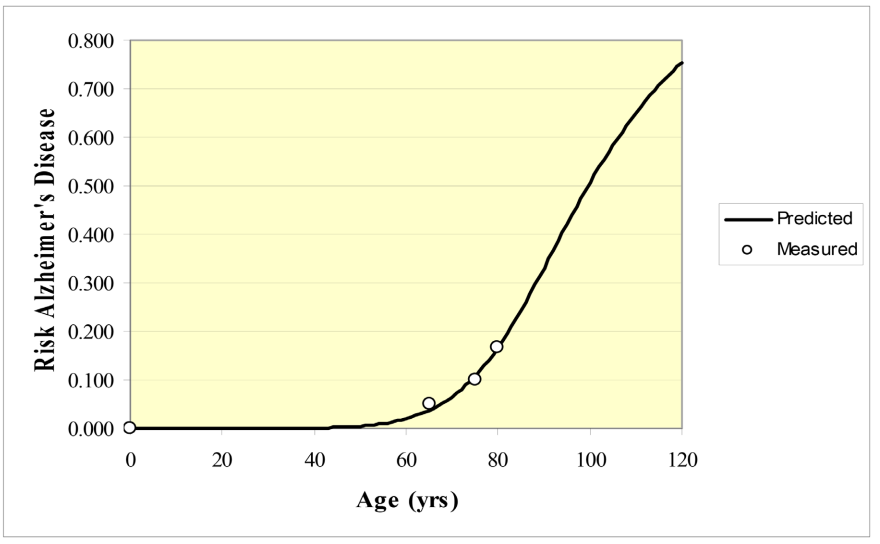

Figure 1. Predicted and measured risk for Alzheimer's disease. Data from 2021 Alzheimer's Disease Facts and Figures [1].

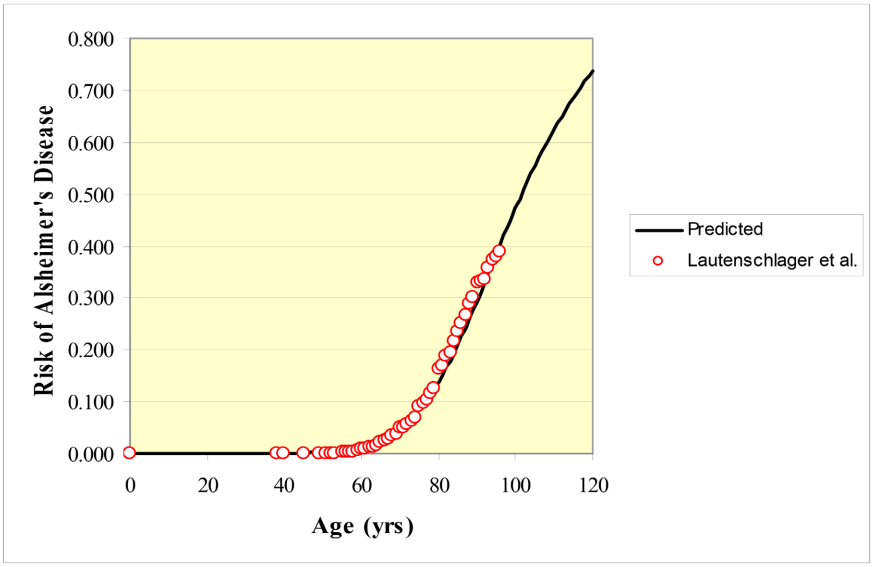

Figure 2. Comparison of risk for Alzheimer's disease for various ages compared to predictions from the Alzheimer's risk model. Data points from Lautenschlager *et al.* [18].

CTE by adjusting the flushing efficiency factor.

2.2. Chronic Traumatic Encephalopathy (CTE)

The next step in development was to consider the damage to brain cells from external effects. It was hypothesized that these effects might reduce the efficiency, F_e, in clearing waste. External factors that are known to increase the risk of Alzheimer's disease include brain trauma from major head injuries, numerous little impacts during football, boxing, and soccer, and compression waves that pass through the brain from explosions.

The following equation (derived in **Appendix C**) was used to estimate the loss of flushing efficiency to include the effect of external stressors on the loss of cells in the glymphatic system:

$$F_e = \left(1 - R_T\right) \mathrm{e}^{-kI_f} \tag{6}$$

where $1 - R_T$ = the efficiency based on the build-up of waste materials in the brain, especially in the front center lobe of the brain that regulates slow-wave sleep

e^{-kI_f} = the efficiency based on the health of brain cells after injury

k = calibration coefficient

I_f = total stressor input

The "2021 Alzheimer's Disease Facts and Figures Special Report" (page 16) [1] reports that the risk of developing CTE increases by 30 percent per year of playing football. This number is based on information provided by Mez *et al.* [35]. While the waste deposits are different for Alzheimer's disease and CTE, the process of development appears to be the same. Incomplete flushing appears to be the process that builds the destructive tau deposits associated with CTE.

An interesting observation is that not all football players or boxers develop the condition of CTE. Some estimates suggest that only about 20 percent develop CTE. One estimate for boxers is that at least 17 percent of boxers develop CTE [19] [36]. Safinia *et al.* [19] also report that "longer careers and higher number of bouts is associated with higher CTE incidence." Omalu ([34] pages 13, 61) in his book, *Play Hard, Die Young: Football Dementia, Depression, and Death*, estimates about 20 percent of boxers develop a form of CTE known as dementia pugilistica. He suggests that about 20 percent of football players will also develop CTE or gridiron dementia. Safinia *et al.* [19] report an estimate that 23 percent of the general population has an APOE4 allele. Are these numbers related?

There is evidence [44] [45] that people having an APOE4 allele significantly fare worse six months and later after brain injury than people without the APOE4 allele. Thus, genetics may be one reason why about 20 percent of boxers and football players develop CTE. The APOE4 allele certainly seems to hinder long-term recovery from brain trauma.

It is assumed at this point that the progression from normal aging or from early stages of Alzheimer's disease to CTE is caused by damage to brain cells from external stressors, such as impacts to the head in football, boxing, soccer,

etc. and/or blast waves that pass through the brain from explosions. Damage to the glial cells should greatly reduce their efficiency in removing waste that leads to a buildup of tau tangles and amyloid β plaque.

To calibrate and test Equation (6), a sampling of people exposed to repeated head impacts and non-impacted people is needed. Russell *et al.* [46] analyzed professional soccer players each matched to three non-players of the same age and socioeconomic status. This design allowed direct analysis of the risk associated with the playing of professional soccer.

They report a risk of 1.6 percent of the matched population control individuals developing the neurodegenerative disease during the study period. The Alzheimer's disease model was run for men only (gender factor = 10.5 and relative fitness = 0.45). The predicted risk of 0.015 (1.5 percent) occurred at age 69 and 1.7 percent occurred at age 70 years. Based on this close agreement, a 70-year age was used for comparisons between predictions and measured soccer data.

Injury input was made by entering 1 for each year that the professionals played soccer. The model summed the years played to obtain the I_f value in Equation 6. After retirement, the input returned to zero, but the summed value was used for I_f for the continued prediction of risks with age. This process is based on the assumption that there is minimal recovery of the flushing system after the damage is done. Professional players obviously have a beginning playing and development of skills in high school or college. A four-year period of playing and using the head was assumed prior to the professional years played. The adjusted years of head impact (**Table 1**) was used as input to the model.

A value of 0.0275 was determined for k in Equation 6. An R^2 value of 0.80 was obtained comparing measured to predicted values. One degree of freedom was lost due to calibration; nevertheless, the results were significant (p = 0.05). Results are shown in **Figure 3**.

If the measured hazard ratio for the 12 years of head impact is eliminated, the R^2 jumps to 0.97. Russell *et al.* [46] do not explain why the 6 - 10 year range of professional play has a higher risk than the 11 - 15 range. One possibility is that defenders, midfielders, and multi-position players with a higher risk of CTE retire before forwards and outfielders. They analyzed the hazard ratio for soccer

Table 1. Risk of neurodegenerative disease for soccer players.

Years Professional Play[1]	Adjusted Professional Years	Adjusted Years of Head Impact[2]	Hazard Ratio[1]	Risk %	Predicted Risk %
0	0	0	1.00	1.6	1.7
< 5	3	7	2.26	3.6	3.3
6-10	8	12	4.61	7.4	5.1
11-15	13	17	4.28	6.8	7.5
> 15	17	21	5.20	8.3	10.0

[1]Data from Russel *et al.* [46]. [2]Four years of impact were assumed prior to professional play.

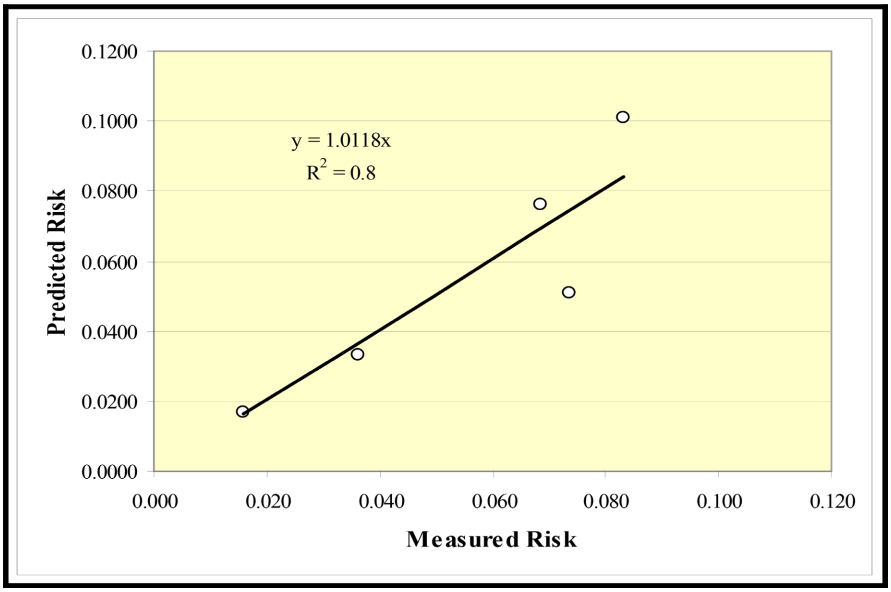

Figure 3. Comparison of measure and predicted risk for neurodegenerative disease in professional soccer players. Data from Russel *et al.* [46].

positions and determined that defender and multiposition had ratios of 4.98 and 4.94 respectively compared to forwards (2.79) and outfielders (3.83). Even with the noise in the measured data, the model appears to be a reasonable and stable system to predict both Alzheimer's disease and CTE resulting from playing soccer.

Next, data for football players were analyzed to further evaluate the CTE model. Mez *et al.* [35] used data collected from three brain banks to determine the odds of developing CTE as a function of years played by football players. Their data do not provide the actual risk of a football player developing CTE. Nevertheless, their data is useful to estimate the risk of developing CTE. **Figure 4** was used to retrieve the log odds as a function of years played. **Figure 4** shows the data and a linear line fit through the log data. The 0.29 slope in the fitted equation is about the same as the 0.3 value reported in their paper and in the 2021 Alzheimer's disease Facts and Figures report [1].

An exponential of the log data odds was used to convert to odds in real instead of log space. This operation reveals that the last few points (especially the largest odds value associated with 20 years of play dominated the log fit equation (**Figure 5**, P e0.3). An exponential equation using a calibration of 0.17 (P e0.17) is a much better fit than a 0.3 calibration for the data for years played less than 16 years.

The data for years played larger than 16 years does not follow the same pattern as less than 16 years. It is unknown if there is a bias in the data selection associated with years played over 16 years or if a second function (P e0.17+) starts to dominate for the higher years played. In either case, the first 15 years of playing football seem to be almost independent in terms of mathematical function from the other points.

The data set also does not have any direct connection to a general population

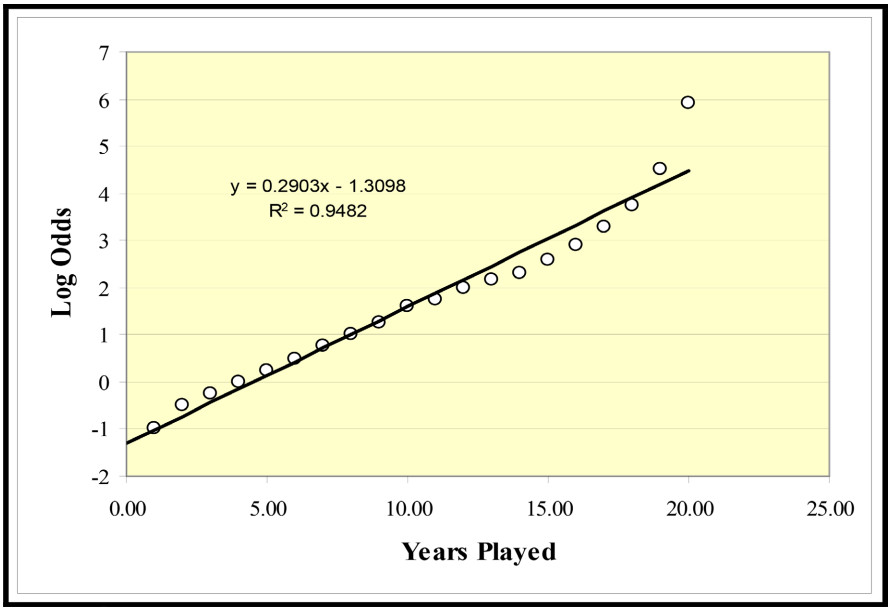

Figure 4. Log Odds data from Mez *et al.* [35].

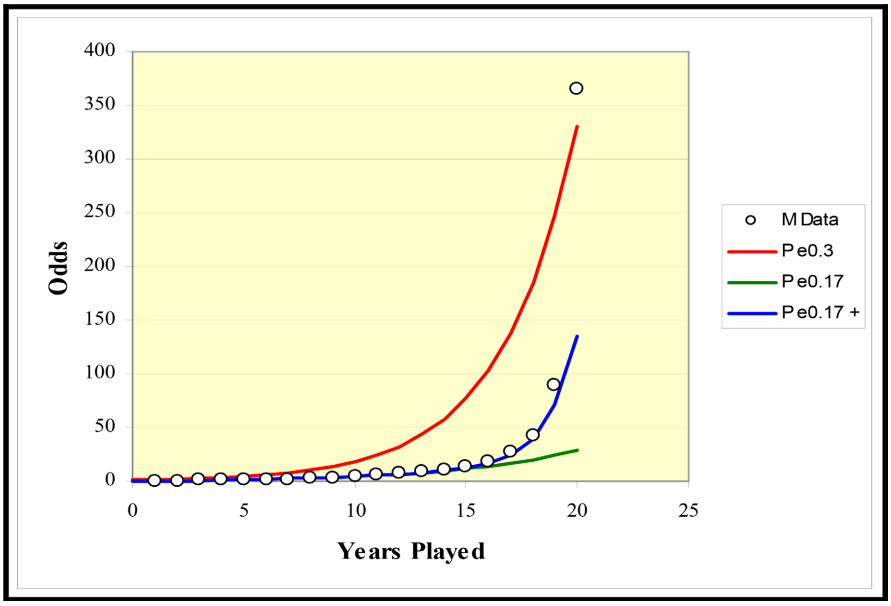

Figure 5. Odds data from Mez *et al.* [35] in normal space illustrating how the maximum odds point causes the model to miss match lower values of odds data. Two other models are shown for the lower values.

of men. The only connection is the odds and years of playing football. On the other hand, there is a strong indication that the risk for CTE increases as a function of years played football.

There may be a way, however, to finesse a general calibration for football players. If we use the suggestion that about 20 percent of football players will develop CTE [34] before they die, we can make a rough calibration if we know the average age of death.

The average age of the football players in the study by Mez *et al.* [35] is 61

years. This age is about the same as the average age at death for football players reported by various websites. This age was used to calibrate and further test the CTE component of the model for football players.

The value for k in Equation (6) that was determined for soccer players was assumed for football players. The model was then run with 20 years of playtime and an input number for injury input. The value for yearly input was varied until a prediction of risk close to 0.2 was obtained at age 61 years. A value of 2.3 of input for each year played for a playtime of 20 years results in predicted risk of 0.208. Based on this rough calibration, each year playing football is 2.3 times more stressful than a year of playing soccer.

An input of 2.3 for each year played was used starting at age 18 (senior year in high school) and continuing for 20 years of active playing. Zero input was used for each year before age 18 and for each year after age 37. The Excel model was programmed to sum the inputs to get a value for I_f for each year. The variable I_f, thus varied from zero to 46 (20 × 2.3) and continued at 46 after age 37.

It is logical that contact sports should reduce the efficiency of the flushing and blood circulation system in the brain affecting the health of the various cells. During impact, the soft tissue of which the brain is made experiences stress/strain changes. This mechanical loading on the tissue cause minor damage to the various cells. It is logical that I_f would be directly related to the amount or number of loading events. Hence,

$$I_f = h\sum S_{yr} \tag{7}$$

where h = hit factor based on number and severity of head impacts

(h = 1.0 for soccer players)

(h = 2.3 for football players)

$\sum S_{yr}$ = sum years played for impact sports

It also seems reasonable that football players might receive 2.3 times more hits and/or more severe hits to the head than soccer players.

There also may be a secondary effect imbedded in contact sports data. The body, including the brain, attempts to heal the damage. While the process is complex, generally there is swelling and inflammation from the healing process. Usually, the benefits of short-term or acute inflammation outweigh the side effects. With contact sports, the process is repeated numerous times and the acute inflammation lingers and tends to exist long-term. Long-term or chronic inflammation is harmful and appears to be another source of damage. The secondary or inflammation damage should also be a function of the amount or number of loading events.

During the testing of this model, the relative risk data were adjusted by dividing the odds data by a calibration constant. The relative risk was adjusted to obtain the least residual error (best R^2 value for the first 15 years of playing football). See Table 2. An $R^2 = 0.97$ as illustrated in Figure 6 was obtained. The relative risk for this match occurred when the odds values were divided by 103. Thus, for 1 to 15 years of playing, the predicted risk from the model matched the

Table 2. Predicted and relative risk of CTE.

Years Played	Log Odds*	Odds	Relative Risk**	Predicted	Predicted??
0				0.004	
1	−1.0	0.37	0.004	0.006	
2	−0.5	0.61	0.006	0.008	
3	−0.3	0.78	0.008	0.010	
4	0.0	1.00	0.010	0.013	
5	0.25	1.28	0.012	0.017	
6	0.5	1.65	0.016	0.022	
7	0.75	2.12	0.021	0.027	
8	1.0	2.72	0.026	0.034	
9	1.25	3.49	0.034	0.042	
10	1.6	4.95	0.048	0.051	
11	1.76	5.81	0.056	0.061	
12	2.0	7.39	0.072	0.073	
13	2.15	8.58	0.083	0.086	
14	2.3	9.97	0.097	0.101	
15	2.6	13.46	0.131	0.117	0.117
16	2.9	18.17	0.176		0.134
17	3.3	27.11	0.263		0.152
18	3.75	42.52	0.413		0.171
19	4.5	90.02	0.874		0.189
20	5.9	365.04	3.544		0.208

*Data obtained from Figure 3 A (Mez *et al*, [35]);**Relative Risk obtained by dividing Odds data by 103 to best match years played 1 - 15; Relative Risk in red exceeds the value of 1.0, the upper limit for probability; Highlighted predicted probability is based on estimates of a maximum lifetime risk of 20%.

shape of the relative risk data well.

For 16 to 20 years of play, the predictions from the model began to mismatch the relative risk data. The extreme point associated with 20 years of play for the relative risk data is 3.544. This number exceeds the upper limit of 1.0 for the probability of developing CTE. If we divide the odds data by the maximum value of 365, then the relative risk for playing football from 1 to 15 years seems to be extremely low; even below the risk of developing Alzheimer's disease for a general population.

The predicted values for 1 to 20 years of playing football and the relative risk excluding the values for playing 17 to 20 years are shown in Figure 7. Predictions for play times of 16 - 20 years are shown in red indicating that these values

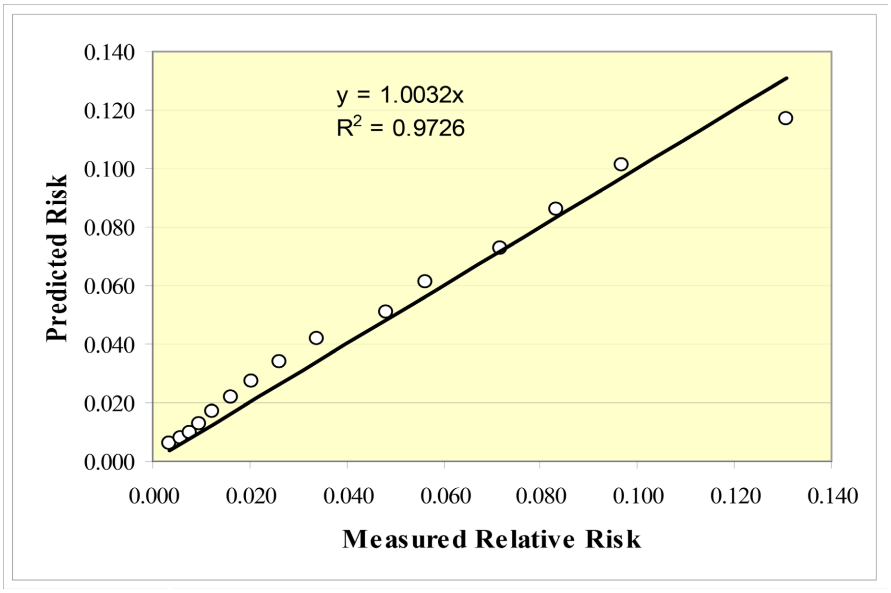

Figure 6. Predicted risk for CTE and the relative risk derived from the odds data of Mez *et al.* [35] for playing 1 to 16 years of football.

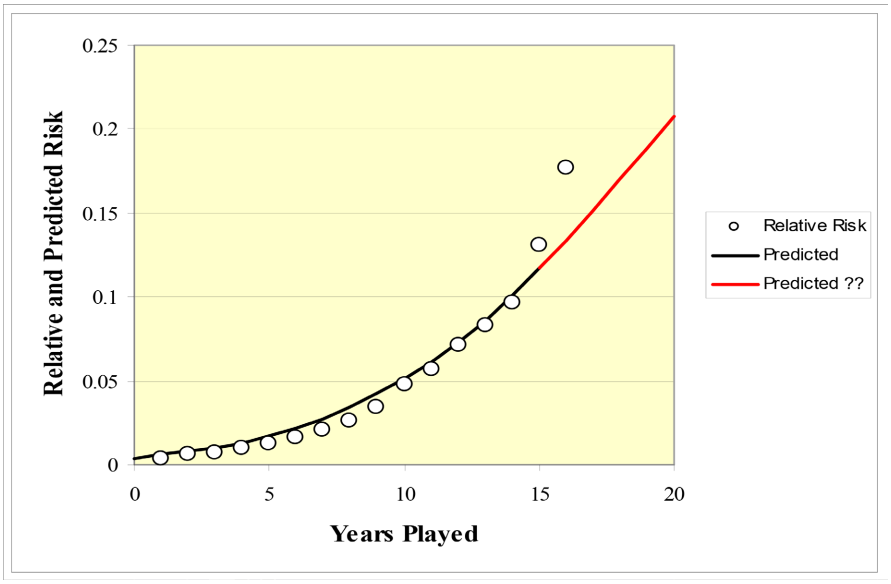

Figure 7. Comparison of the predicted risk for CTE and relative risk data derived from Mez *et al.* [35] for 1 to 20 years of playing football. Predicted risk expressed in red are not verified with relative risk data.

are not verified with the relative risk data.

While the R^2 value and significance level are acceptable, the failure to have an agreement between the relative and predicted risk for the most extreme years of play (16 - 20) is a concern. It is certainly possible that donations to the brain bank were not random in terms of years played. It seems likely that people making donations would be most likely to donate the brains of people with the most extreme symptoms of a problem.

Based on the model presented, the development of Alzheimer's disease and

CTE appears to be governed by the same process. In addition to the loss of slow-wave sleep that reduces flushing of waste, injury to various brain cells appears to further reduce flushing efficiency and leads to an increase in deposits of tau tangles throughout much of the brain.

2.3. Depression

Another medical problem, depression, seems to be associated with the development of both Alzheimer's disease and CTE. Early-onset of depression seems to increase the risk of developing Alzheimer's disease by about two times [29].

Data for depression and risk for Alzheimer's disease is fuzzy in nature with some studies in apparent conflict with other studies. There is uncertainty if depression causes an increase in risk for Alzheimer's disease or if Alzheimer's disease leads to depression. The nature of late-onset depression and Alzheimer's disease is especially unclear. The increased association between late-onset depression and Alzheimer's disease is not considered in the model at this time.

Early-onset depression, however, appears to increase the risk for Alzheimer's disease. Byers and Yaffe [29] in their discussion of early-onset depression conclude that "early-onset of depression is significantly associated with risk of developing dementia." They state the following:

> Four of the 5 studies were longitudinal and suggest that early-onset of depression, as well as the duration and frequency of depression, were associated with a 2 to 4-fold increased risk of developing dementia…The second study demonstrated a strong association between the number of depressive episodes (*i.e.*, recurrent depression) and the risk of dementia over a median follow-up time of 24 years, suggesting a dose-dependent relationship of cumulative depression episodes to the risk of dementia.
> …One cross-sectional (case-control) study suggests that a history of depression even 25 years prior to AD onset is significantly associated with an almost 2-fold increase in the likelihood of developing AD…

To further complicate the modeling of depression effects on the risk of Alzheimer's disease, there is evidence that some antidepressants can reduce the development of risk for Alzheimer's disease [38]. Kessing *et al.* [38] report a relative risk of 0.66 for Alzheimer's disease for older antidepressants compared to newer antidepressants. Furthermore, continued use of the older antidepressants was implied with two or more prescriptions of older antidepressants being more effective than only one prescription. If a person has depression and takes prescriptions of antidepressants until the depression is in remission and then quits medication, is the risk for Alzheimer's disease reduced? If it is reduced, is it because of treatment? Is it due to the antidepressant or lack of depression for the rest of life? Obviously, questions like these complicate the understanding of data.

In a study at Duke University [47], aerobic exercise as a treatment was compared to a serotonin treatment (selective serotonin reuptake inhibitor, SSRI, sertraline [Zoloft]). Both had similar effects with a relatively rapid response to

treatment then flattened to a relative slow improvement over a long period of time. The aerobic treatment can be modeled with changes in VO_{2max}. They measured VO_{2max} before and after the period of study and verified that the exercise increased VO_{2max}. Obviously, the medication did not change VO_{2max}; thus, this study implies that the change is related to something affected by both exercise and the medication.

Exercise and antidepressants both tend to "increase the activity of the so-called monoamine neurotransmitters: norepinephrine, dopamine, and serotonin" ([48] pages 115 and 121). It is also generally understood that depression often affects sleep resulting in too little or too much with poor sleep efficiency and probably reduced slow-wave sleep. For the model development, it was assumed that like aerobic exercise depression and slow-wave sleep are related. A slow-wave efficiency factor, d_3, was added to the prediction of slow-wave sleep. Without depression, the factor has a value of 1.0. With depression, this factor or multiplier is less than 1.0 depending on the severity of depression. It was hypothesized that depression may build up from stress in life or reduce in response to treatment and reduced stress in life.

There is evidence, at least in rats, that stress changes neurogenesis in the hippocampus area of the brain [49]. As neurogenesis (gray matter development) decreases and oligodendrogenesis (white matter development) increases, an imbalance in the ratio of gray to white matter occurs, which may explain in part how stress increases the risk of depression and the reduced sleep quality that often develops in parallel with depression. It is common knowledge now from various research studies that aerobic exercise in rodents and humans slowly increases neuron regeneration—a counter measure to depression as observed in the Blumenthal *et al.* [47] study.

Because stress or aerobic exercise can change and be managed over time, the depression component or more general emotional stress component of the Alzheimer's disease model was designed to allow a slow recovery when stress is removed or antidepressant management is used.

A column in Excel was created to input zero for no depression and a number between 0 and 4 for each year depressed with 2 as an average degree of depression. The user inputs (a number between 0.0 and 4.0) are based on the work of Byers and Yaffe [29]. The model uses a weighted average between the previous depression efficiency factor and the new input to compute a new efficiency factor. The weighted average essentially provides an exponential decay function to reduce slow-wave sleep over time due to depression or a saturating exponential to increase efficiency back to 1.0 when treatment is effective. The following equation is used:

$$d_3 = d_{3old}\, m + \left(1 - C_{ES} E_S\right)\left(1 - m\right) \tag{8}$$

where d_3 = current calibration for slow-wave sleep

d_{3old} = previous calibration (year before)

C_{ES} = calibration to adjust depression severity to the risk of developing

Alzheimer's disease (0.22)

E_S = new input associated with depression severity (value of number is roughly the increase in the risk of developing Alzheimer's disease

m = weight for old calibration (0.98)

The weight value of 0.98 is the same as was used by your author to model the change in VO_{2max} over a period of time of active bed rest in a study by Saltin *et al.* [50]. This same value may be a coincidence or both may be related to passive changes in metabolism. The value for C_{ES} of 0.22 was determined by an input of 2.0 for E_S for each year starting at age 20 going to age 70 and approximately doubling the risk for Alzheimer's disease at age 70. If depression starts later in life, there are fewer years (less dose of depression) to increase Alzheimer's disease.

After this rough calibration, the model was run for depression starting at different ages to see the nature of the predicted risk for Alzheimer's disease. The model also was run for depression starting at age 20 and ending at various ages. Results are shown in **Figure 8**. These simulations produced about the same level of risk for Alzheimer's disease in terms of years depressed more or less independent of how the depression years occur. The results seem to match the dose suggestion by Byers and Yaffe [29]. Also, the odds value for 20 years of depression followed by no depression for the following 30 years compared to 50 years of depression is 0.65 compared to the report of 0.66 from Kessing *et al.* [38]. The model has the potential to adjust for successful treatment by turning off or reducing the severity of the depression input.

It may also be possible to use the emotional stress input to link sexual assault and other traumatic experiences to the increased risk of developing Alzheimer's

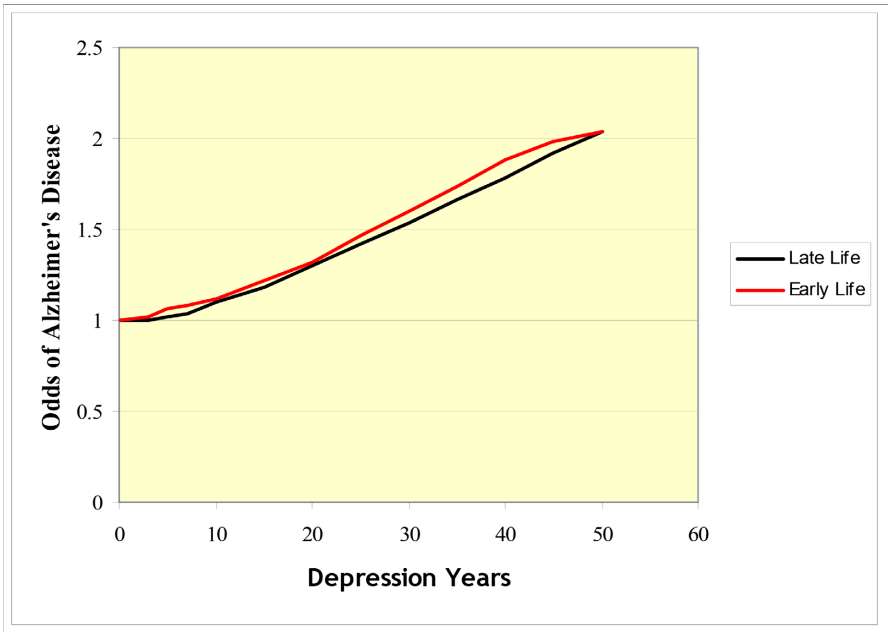

Figure 8. Illustration of predicted odds of developing Alzheimer's disease in association with years of depression.

disease later in life. Thurston *et al.* [51], have related sexual assault to poor sleep, depression, and anxiety. Thurston *et al.* [52] have also related sexual assault and other traumas to white matter hyperintensities among midlife women. These white matter hyperintensities that show up on neuroimages are normal in older adults, but women who have been traumatized early in life tend to have an increased volume of these white matter spots. Further research is needed to provide sufficient data to calibrate the emotional input in the Alzheimer's disease model to predict this type of input on the risk of developing Alzheimer's disease.

No data were found that directly measured a dose effect of depression on the risk of Alzheimer's disease as shown in **Figure 8**. Green *et al.* [15], however, reported data relating the interval between the onset of depression and the onset of Alzheimer's disease. This information was used in conjunction with the simulated data used to prepare **Figure 8** to provide a rough verification of the depression model and calibration used to predict the increased risk of Alzheimer's disease.

The average age of people in their study was 70 years rounded to the nearest year. This age matches the 70-year age used to determine the odds of Alzheimer's disease in **Figure 8**. Their data are shown in **Table 3** along with the predicted values based on the average of the individual odds associated with each row criteria used by Green *et al.* [15]. A comparison of measured and predicted odds is shown in **Figure 9**.

An R^2 value of 0.70 was obtained by comparing measured and predicted values. The results were statistically significant ($p = 0.05$). It appears from these results that using the input of emotional stress (a number between 0 and 4 for depression) is a reasonable way to model the effects of depression on the development of Alzheimer's disease.

Green *et al.* [15] raised the question of how depression causes an increased risk for Alzheimer's disease: "Is there something about depression that is potentially 'toxic' to the brain and predisposes to a later vulnerability to AD?" Based on the present model, the answer may be as simple as changes in sleep quality.

Table 3. Comparison of measured and predicted odds.

Interval (yrs) Depression Years	Measured OR[1]	Predicted OR (Average of Odds on Right)	Depression Years						
			10	15	20	25	30	35	40
			Predicted Odds Associated with Depression Years						
>5	1.39	1.43	1.10	1.18	1.30	1.42	1.54	1.66	1.78
>10	1.34	1.48		1.18	1.30	1.42	1.54	1.66	1.78
>15	1.58	1.54			1.30	1.42	1.54	1.66	1.78
>20	1.70	1.60				1.42	1.54	1.66	1.78
>25	1.71	1.66					1.54	1.66	1.78

[1]Measured data from Green *et al.*, [15].

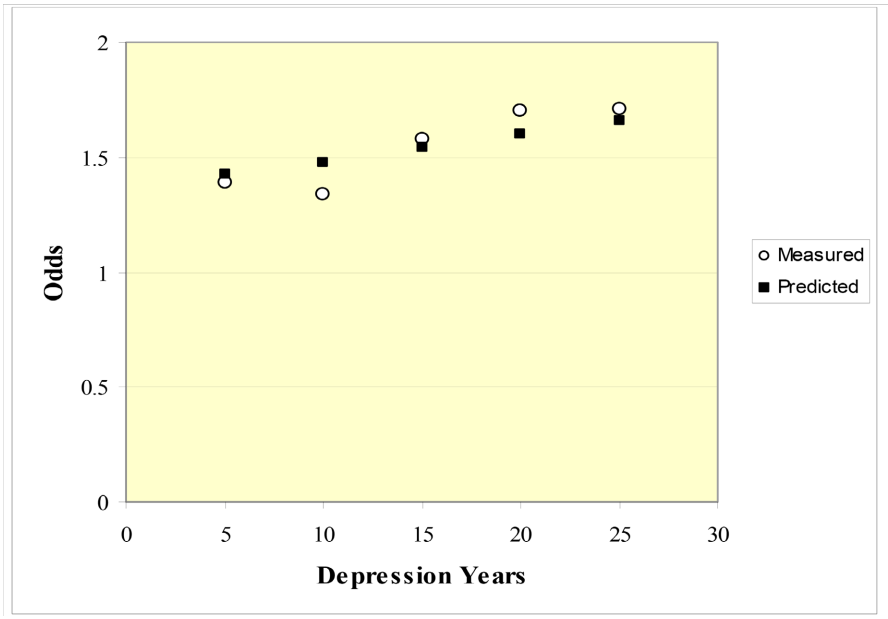

Figure 9. Measured and predicted odds as a function of depression years (predicted values) and interval between depression onset and Alzheimer's disease onset (measured values).

3. Results

The results comparing estimates from the model to data reported in the literature were presented as each component of the model was developed. The general population result is shown in Figure 2. The model is not independent of this data set; however, both the model estimates and this data set are in agreement with the risk reported by the Alzheimer's Association [1].

Results for soccer players with CTE are shown in Table 1 and Figure 3. This data set compared men soccer players to non soccer players of the same social and economic status. The results indicate a linear relationship between odds of developing CTE and years played.

A second data set considering years played for football was also considered. This data set did not have a comparison to non-football players of the same social and economic status. Nevertheless, this data set was used for a relative comparison. The first 15 years of playing football followed a linear increase with years played. The remaining five years deviated from the pattern of the first 15 years. The calibration by Mez [35] seemed to be highly influenced by these points in log space. The Alzheimer's Association [1] seems to have used this calibration for their reporting, which seems to be an exaggeration of the real risk. The results from the present analysis indicate that playing professional football has about 2.3 times higher risk for each year played compared to soccer.

Finally, the model predicts that untreated depression will increase the risk of developing Alzheimer's disease as a function of dose or years depressed. The age at which depression starts does not seem to be a factor other than an early start has the potential to increase the number of years depressed.

4. Discussion

A mathematical model was developed to estimate the risk of developing Alzheimer's disease as a function of age. Predictions from the model matched reported risk values published in the literature with an R^2 of 0.99, which was highly significant ($p < 0.001$). The model includes a gender factor and a relative fitness that adjusts VO_{2max} that in turn is used to adjust the amount of slow-wave sleep. Variations in these variables were not tested with Alzheimer's data. The model does predict that the risk of developing Alzheimer's disease is highest for the least aerobically fit (lowest maximum oxygen uptake) people. It also predicts that women are at a higher risk of developing Alzheimer's disease than men.

Predictions with the current model used a relative fitness average for a person's lifetime. The model can evaluate the effects of increased or decreased relative fitness as a person ages using a yearly input of relative fitness. There is much potential to use maximum oxygen uptake as a management tool to predict the benefits of aerobic exercise to delay or at least slow the progression of Alzheimer's disease.

The model is based on the concept that as sleep is reduced with age or lack of fitness, the efficiency of the central front lobe in the brain starts to deteriorate as amyloid β begins to build up in this part of the brain. As this part of the brain becomes less efficient, slow-wave sleep is reduced and the time used to wash away waste products is reduced leaving more waste material, such as amyloid β deposited in the brain. This process cycles each day slowly leading to the development of Alzheimer's disease.

There is now growing evidence [43] that genetics through APOE alleles affect the generation of amyloid β. If genetics affect the generation of amyloid β, then it is logical that genetics affect the calibration of β_0/β_R.

The generation of amyloid β goes up as cholesterol goes up. While it may be possible to reduce the generation of amyloid β by reducing cholesterol, the brain needs some cholesterol for other functions. Thus, the goal should be to control but not eliminate cholesterol. It may be possible to adjust the model for cholesterol management through β_0/β_R. We can think of β_0/β_R as the risk associated with the generation of amyloid β when there is no flushing. It is the potential for developing Alzheimer's disease. Anything that affects the metabolism of brain cells probably affects the calibration value for β_0/β_R.

In fact, epidemiological studies have shown a strong decrease in the incidence of Alzheimer's disease when patients are treated with statins, such as simvastatin and lovastatin [53] [54] [55]. Fassbender *et al.* [53] provided controlled research with guinea pigs that support the epidemiological findings. Guinea pigs treated with high levels of simvastatin had a major reduction of cerebral amyloid β levels in their cerebrospinal fluid.

Values for coefficients A_1 and β_0/β_R were calibrated to optimize the fit to published Alzheimer's risk data. In addition to providing the proper limits or boundary conditions, Equation (5) with the two coefficients, A_1 and β_0/β_R, can be used

to consider other variables. It is now evident that the production rate of amyloid β occurring at the cellular level is a function of cholesterol level in brain cells [43] [54]. Various satins lower cholesterol in the blood and the cerebrospinal fluid [43] [53]. In general, treatment with satins lowers the risk of the development of Alzheimer's disease by 60 to 70 percent [54]. It should be possible to calibrate β_0/β_R as a function of cholesterol management.

Because the process of generating amyloid β as a function of cholesterol involves APOE alleles, it also appears that the β_0/β_R coefficient may be a good place to calibrate the Alzheimer's model to include the effects of genetics (APOE4: 0, 1, or 2 alleles). Table 4 provides values for β_0/β_R based on some of the odds reported in the literature.

It has been observed that people with higher levels of education and who use their brains in work have less risk of developing Alzheimer's disease [56]. Sometimes this effect is referred to as cognitive reserve [1]. People who are engaged mentally in education and work may have a higher number of brain cells of various kinds with less production of amyloid β than those who coast through life without mental challenges. The coefficient, β_0/β_R, in Table 4 was computed using the model and adjusting the β_0/β_R value to obtain the odds value reported in the associated reference. Age 70 years was used for this analysis. It is uncertain, however, which of the two coefficients, A_1 or β_0/β_R, should be used to consider cognitive reserve.

As stated in the introduction to this article, the development of Alzheimer's disease is complex and seems to be related to various causes. For example, Hussein [26] provides a strong argument that inflammation may be a major factor in the development of Alzheimer's disease. If inflammation is a factor in brain health, then it may be possible to consider this variable through the I_f variable in Equation 11. An acute attack would be considered in terms of the years affected

Table 4. Values of β/βR to adjust the calibration of the Alzheimer's disease model for a few additional variables.

Odds	β_0/β_R	Variable	Reference
0.35	0.0135	Satin medication	Wolozin *et al.* [54]
0.63	0.0235	CR - high	Dekhtyar *et al.* [56]
1.00	0.0350	CR - moderate	Dekhtyar *et al.* [56]
1.34	0.0460	CR - low	Dekhtyar *et al.* [56]
0.80	0.0290	APOE4 - high CR	Dekhtyar *et al.* [56]
1.77	0.0590	APOE4 - moderate CR	Dekhtyar *et al.* [56]
2.85	0.0880	APOE4 - low CR	Dekhtyar *et al.* [56]
3.0	0.0915	APOE4	2021 Alzheimer's Disease [1]
10	0.2130	2 APOE4	2021 Alzheimer's Disease [1]

CR = cognitive reserve (years of education and use of brain in work).

starting at the age when the inflammation began.

An example of a possible dose evident association between inflammation and Alzheimer's disease was tested with data from Gofrit *et al.* [24]. They report in their **Table 1** a mean age for patients diagnosed with bladder cancer and given BCG as a treatment at 67.5 years. The mean age diagnosed and not given BCG was 69.0 years. They also report the mean age at follow-up who received BCG as 78.7 years. For the non BCG treatment, the mean age at follow-up was 75.9 years. Based on this information, the Alzheimer's model was run and the predicted data were analyzed from 68 to 76 years. Subtracting the Alzheimer's disease prediction for 68 years from the 76-year prediction yielded an increase of 2.3 percent. The simulation was run for men (gender factor of 10.5). Gufrit *et al.* [24] report an increase for the treated men group of 2.47 percent. The fact that the group treated with BCG closely matches the percentage of 2.3 from the simulation provides evidence that BCG may have removed the inflammation threat.

The model was run again with injury input in units of years affected starting at age 68 and ending at age 76 years. The input was varied until a match to the reported 9.16 percent increase was obtained. An input of 5.2 for h in Equation 7 from ages 68 to 76 produced an increase of 9.2 percent. These results do not prove that an inflammation effect on Alzheimer's disease is a dose response process, but they provide evidence that the process is feasible—even likely. The model provides a new way to look at the process of how infections and inflammation may influence the development of Alzheimer's disease.

A derivation was provided in **Appendix C** that relates F_e to the fraction of brains cells that function after damage from impacts to the head, such as playing soccer or football. This equation was calibrated using data provided by Russell *et al.* [46]. Predictions matched measured risk values with an R^2 of 0.80, which was significant ($p = 0.5$). A second data set [35] was also used to relate the model to the risk of playing football. Predictions for the first 15 years of playing football matched the relative risk of CTE for football players with and R^2 of 0.97, which was also significant ($p < 0.001$). The variable h was used to adjust for different levels of injury.

While the calibration of the CTE component of the model for football is not considered precise, the results seem reasonable. More importantly, the model provides a mathematical framework to explain how both Alzheimer's disease and CTE develop. The model is robust with stable boundaries of probability between 0 and 1.

It may be possible to relate other brain injury types, such as brain trauma or exposure to pressure waves that pass through the brain to the calibration years affected. The current model is not designed to predict immediate damage from these events, but it may provide a process to predict the long-term effects after injury.

Finally, this model describes the process that relates to both the development

of Alzheimer's disease and CTE. Both developments seem to be related to slow-wave sleep. Both develop after a period of time. Alzheimer's disease alone seems to start with the buildup of amyloid β. Other factors, such as inflammation, genetics, or mental stress may also initiate or at least accelerate the process. CTE seems to be associated more with the buildup of tau tangles. While the process for CTE may start from the mechanical or physical stress on brain cells, the development over time appears to be related to the reduced efficiency of the flushing system. This current work only describes the development after the process starts. Equation 3 was not used in the current model for estimating the risk of developing Alzheimer's disease or CTE. The equation contains the same flushing function as used in Equation (5). The τ_0 variable is probably a function of the damage that occurs to glial and other cells in the flushing system. This would explain why CTE seems to be associated with tau tangles more than amyloid β. Alzheimer's disease plus additional secondary damage from tau tangles seems to be a reasonable description of CTE patients.

5. Conclusion

The development of this article focused on slow-wave sleep. This article and Excel model only evaluated the system for average conditions of fitness and the natural decline of slow-wave sleep with age and the development of Alzheimer's disease and CTE. It is an easy step to expand the model to reduce slow-wave sleep for other reasons, such as restricting sleep due to work pressure or reducing sleep quality due to night work or variations in the circadian cycle. An obvious and major factor that reduces slow-wave sleep is sleep apnea. A model that considers both sleep and other factors that affect brain health should be a valuable tool to better understand and to some degree slow the development of Alzheimer's disease and CTE.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Appendix A. Equation to Estimate Waste Accumulation in Brain after One Night of Sleep

Cleaning or flushing processes generally can be described as a first-order differential equation that produces an exponential decay equation when integrated over a time variable. The flushing of waste from the brain primarily occurs during a slow-wave sleep cycle. The time variable for a night of sleep is the total time of slow-wave sleep. The equation can be derived starting with the following differential equation:

$$\frac{\mathrm{d}W}{\mathrm{d}S_W} = -A_1 F_e W \tag{A1}$$

where W = waste products remaining in the brain

A_1 = calibration coefficient

F_e = flushing system efficiency

S_W = time in slow-wave sleep during a night of sleep

Next, we can separate variables:

$$\frac{\mathrm{d}W}{W} = -A_1 F_e \mathrm{d}S_W \tag{A2}$$

Integration from the beginning (W_0 = production of waste) to ending limits can be used to eliminate the differential variables:

$$\int_{W_0}^{W_F} \frac{\mathrm{d}W}{W} = -A_1 F_e \int_0^{S_{WF}} \mathrm{d}S_W \tag{A3}$$

Integration yields the following:

$$\ln W_F - \ln W_0 = -A_1 F_e S_{WF} \tag{A4}$$

Rearrangement results in

$$\ln \frac{W_F}{W_0} = -A_1 F_e S_{WF} \tag{A5}$$

Taking the exponential of both sides results in

$$\frac{W_F}{W_0} = \mathrm{e}^{-A_1 F_e S_{WF}} \tag{A6}$$

Rearrangement yields an equation to estimate the daily amount of waste remaining in the brain after sleep is completed:

$$W_F = W_0 \mathrm{e}^{-A_1 F_e S_{WF}} \tag{A7}$$

Appendix B. Slow-Wave Sleep Model

Sleep is a cyclic process starting with stage 1, a transition from awake to sleep. Stage 2 occurs next. During stage 2, communication occurs between the hippocampus (the part of the brain that processes and stores short-term memory) and the front center lobe of the brain that provides long-term memory. The trivial unimportant memory information is discarded and the perceived important information is transferred especially during sleep spindles and slow waves ([2]

pages 110-114). Stages 3 and 4 are slow waves (brain waves) relative to the other sleep stages. Stage 4 has more amplitude in the wave than stage 3. The final type of wave during sleep is REM (Rapid Eye Movement) where the brain is active, often dreaming, and has a similar wave form as awake. In a young adult, a cycle typical starts with stage 1, then stage 2, then stage 3, followed by stage 4, then back to stage 2 followed by REM. A cycle takes about 90 minutes. A total of about five cycles typically occurs for a total sleep time of about 450 minutes plus a few minutes of time-awake disruptions. A typical young adult needs about eight hours of sleep—more if they are physically active. In older adults, time-awake increases as much as 90 minutes, reducing actual sleep to 6.5 hours or less per night.

Total time in slow-wave sleep is of interest in this Alzheimer's disease risk model because of the linkage between slow-wave sleep and the flushing of waste materials from the brain. Gregory [57] developed an equation that predicts the increase in slow-wave sleep total as sleep progresses. The equation is

$$S_{WT} = \frac{d_1}{d_2}\left(1 - e^{-d_2 N_T}\right) \tag{B1}$$

where S_{WT} = total time of slow-wave sleep

d_1 = variable that is a function of maximum oxygen uptake (VO_{2max})

d_2 = decay rate (1.1)

N_T = number of cycles completed

Maximum oxygen uptake, VO_{2max}, which will be associated with slow-wave sleep, decreases as a linear function of age as follows:

$$VO_{2max} = 107.4\,RF\left(1 - \frac{A}{120}\right) + G \tag{B2}$$

where VO_{2max} = maximum oxygen uptake ($ml \cdot kg^{-1} \cdot min^{-1}$)

RF = relative fitness (fraction of upper limit)

- (1.00) upper limit, Olympic class skier or runner
- (0.82) approximate upper limit for endurance trained
- (0.67) endurance trained
- (0.50) active (upper boundary for sedentary)
- (0.45) estimate for control or average population (1/4 endurance trained & 3/4 sedentary)
- (0.38) sedentary
- (0.22) approximate lower limit for sedentary
- (0.00) non active bed rest
- A = age (years)
- G = gender coefficient (males: 10.5; females: 3.5) $ml \cdot kg^{-1} \cdot min^{-1}$

This equation describes the effect of age for both males and females through the gender factor. The slope is the same for both males and females at the same relatively fitness. Predictions from Equation (B2) matched the measured values for women [58] with an $R^2 = 0.85$ and for men [59] with an $R^2 = 0.75$. Both results were highly significant using t distribution to predict the probability of type

I error ($p < 0.001$). The various relative fitness descriptions and values are based on these two data sets comparing the measured fitness of runners to sedentary people.

Next, data for slow-wave sleep and age were obtained from the literature as shown in Table B1. A value of 1.1 was used for d_2 in Equation (B1). Assuming a 90-minute average cycle, the number of cycles was estimated from the measured sleep time. A value for d_1 was obtained and listed in Table 1 as a measured value. Values for VO_{2max} were estimated using a relative fitness (RF) of 0.45 for average fitness. These values are listed in Table B1. The following equation was developed to predict d_1:

$$d_1 = \frac{0.0000168}{\left(VO_{2\max}\right)^3} \tag{B3}$$

This equation predicted d_1 with an R^2 equal to 0.84. This result was highly significant ($p < 0.001$). Predicted values are shown in Table B1. The relationship is shown in Figure B1.

While the calibration of Equation (B3) was based on a relative fitness of 0.45, the curves generated for sedentary (RF = 0.38) and active (RF = 0.50) seem to

Table B1. References and measurements for slow-wave sleep.

Source	Age (years)	Slow Wave (hours)	VO_{2max} ml.kg^{-1}.min^{-1}	d_1 Measured	d_1 Predicted
Coble [60]	7.4	2.17	52.35	2.40	2.41
Coble [60]	9.4	1.87	51.54	2.10	2.30
Coble [60]	11.4	1.63	50.74	1.80	2.19
Coble [60]	13.0	1.57	50.09	1.70	2.11
Coble [60]	14.8	1.25	49.37	1.40	2.02
Gaillard [61]	20.0	2.22	47.28	2.40	1.78
Hayashi and Endo [62]	20.9	1.33	46.91	1.63	1.73
Gaillard [61]	23.0	1.78	46.07	2.00	1.64
Gaillard [61]	26.0	1.27	44.86	1.40	1.52
Gaillard [61]	29.0	1.38	43.65	1.50	1.40
Banks [63]	30.4	1.33	43.09	1.37	1.34
Gaillard [61]	44.0	0.97	37.61	1.10	0.89
Reynolds [64]	64.6	0.28	29.31	0.30	0.42
Reynolds [64]	65.2	0.05	29.07	0.05	0.41
Reynolds [65]	70.1	0.52	27.10	0.58	0.33
Reynolds [64]	73.5	0.05	25.73	0.05	1.29
Reynolds [64]	73.8	0.11	25.61	0.13	0.28
Hayashi and Endo [62]	82.1	0.25	22.26	0.27	0.19

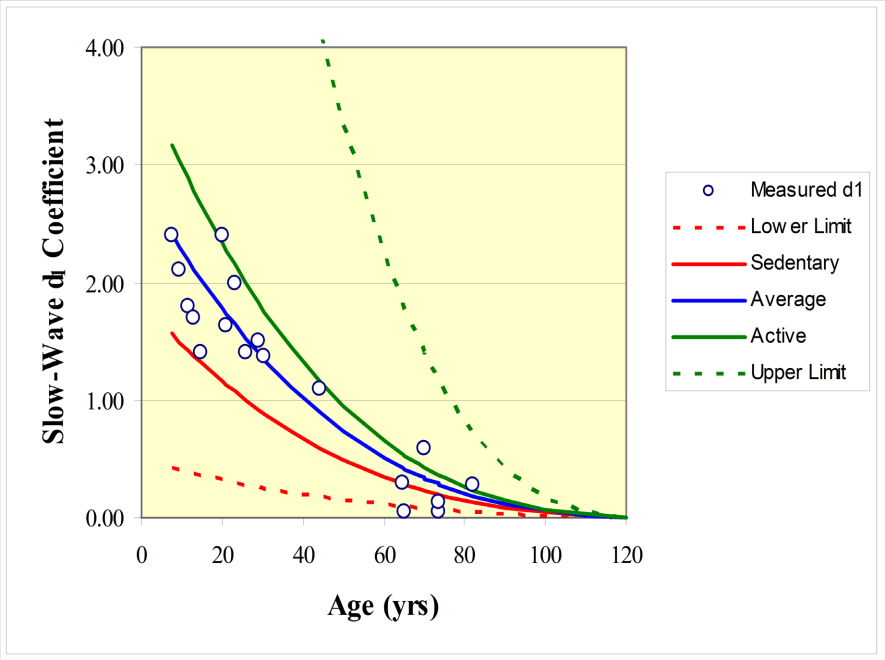

Figure B1. Relationship between slow-wave sleep coefficient, age, and relative fitness. Data from **Table B1**.

be reasonable boundaries for most of the measured data points. Equation (B3) coupled with Equations (B1) and (B2) provide a way to consider lifestyle effects on slow-wave sleep.

To use Equation (B1), we also need an estimate of the number of cycles used for sleep. Total sleep time with the assumption of 90-minute cycles or measured cycle number when reported was used with the sleep data sources listed in **Table B1** to develop the following equation for cycle number as a function of age:

$$N_T = 5.26 - 0.0212A \tag{B4}$$

This linear function from ages 7 to 80 years of age fit the cycle number data well ($R^2 = 0.85$; $p < 0.001$).

Appendix C. Estimating Flushing Efficiency

It is assumed that flushing efficiency depends on the health of the glymphatic system including glial cells that are part of the flushing system. The change in the number of cells damaged per change in impact from stressors should be a direct function of the total number of undamaged cells available to be damaged:

$$\frac{\mathrm{d}C}{\mathrm{d}i} = k\left(C_T - C\right) \tag{C1}$$

where C = number of cells damaged

i = unit impact of external stressor

k = calibration coefficient

C_T = initial total number of undamaged cells

We can now separate variables to prepare for integration to eliminate the dif-

ferentials:

$$\frac{\mathrm{d}C}{C_T - C} = k\mathrm{d}i \tag{C2}$$

To prepare for integration, let $X = C_T - C$. The differential $\mathrm{d}X = -\mathrm{d}C$. Next, we multiply both sides of the equation by −1 to make $\mathrm{d}X = -\mathrm{d}C$, then integrate:

$$\int_{C_T-0}^{C_T-C_f} \frac{\mathrm{d}X}{X} = \int_{0}^{I_f} -k\mathrm{d}i \tag{C3}$$

where C_f = final number of cells damaged

I_f = total stressor input

The results after integration are

$$\ln\left(\frac{C_T - C_f}{C_T - 0}\right) = -kI_f \tag{C4}$$

We can now take the exponential of both sides to obtain

$$\frac{C_T - C_f}{C_T} = \mathrm{e}^{-kI_f} \tag{C5}$$

The number of the undamaged cells over the initial number of cells should be a reasonable estimate of the efficiency of the system controlled by these cells. Thus, the flushing efficiency, F_e becomes

$$F_e = \left(1 - R_T\right)\mathrm{e}^{-kI_f} \tag{C6}$$

where $1 - R_T$ = the efficiency based on build-up of waste materials in the brain, especially in the front center lobe of the brain that regulates slow-wave sleep

e^{-kI_f} = the efficiency based on the health of brain cells after injury

In other words, the flushing efficiency, F_e, is assumed to be the product of two efficiencies: efficiency considering the buildup of toxic waste in the brain and the efficiency of the brain cells (damage or inclusion of tau tangles in neurons and glial cells and damage to the vascular system that provides nutrients to the cells).