Alzheimer's Disease: An Analysis of Gender Effects

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Abstract

Alzheimer's disease is a dreaded outcome that affects both men and women in later years of life. While root causes of this form of dementia are not clear, various factors are known that contribute to the risk of development and the reduction in risks based on gender and our choices in life. This paper evaluates the various factors that affect the risks of developing Alzheimer's disease as we age. The focus of this paper is gender considerations in a mathematical model programmed in Excel. The model was first presented by Gregory [1] and was calibrated on one of the original population data sets with 50 - 50 male and female participants. This model overpredicted the risks for women and underpredicted the risks for men. A solution to this problem was found based on published values of sex hormones for men and women. Based on the expanded current model, two major factors contribute to the gender differences in predictions: gender factor values (10.5 ml·kg^{-1}·min^{-1} for men and 3.5 ml·kg^{-1}·min^{-1} for women) used in VO$_{2max}$ equations and a sex hormone factor that changes as hormones change for men and women with age. Smoking differences associated with gender and the risk associated with smoking was added to the model. Cognitive reserve based on education differences between men and women was also added. These are minor components compared to hormone effects. The expanded model includes an input for unsaturated fat diets and cholesterol reducing medications and use of Viagra by men that is known to reduce risk of developing Alzheimer's disease. Predictions from the expanded model closely matched measured values from age 50 through age 95 for each gender with R^2 values of 0.99, which were highly significant (p = 0.001). The expanded model predictions matched the reduced lifetime risk for men and women associated with a data set that included a population with the opportunity to use statins and Viagra. The expanded model seems to work well for both men and women.

Keywords

Gender Effects, Alzheimer's Disease, Dementia, Mathematical Modeling,

Statins, Viagra, Cholesterol, Unsaturated Fat Diets

1. Introduction

It is relatively well established that over a lifetime women have a higher probability of developing Alzheimer's disease than men. The reason is still largely unknown. Chene *et al.* [2] have summarized the problem as follows:

> Among other potential risk factors, a link with gender has been particularly contentious.

They listed and discussed possible factors that might explain why women have higher risk, such as smaller brain size, sex hormones, and cognitive reserve. They failed to mention that women on average are shorter, lighter in weight, and have less potential for maximum oxygen uptake [1] [3] [4]. Women are proportionately smaller than men. So, brain size might or might not explain why women have a higher risk for Alzheimer's disease.

Women on average live about 10 percent longer than men. Vina *et al.* [5] present evidence that sex hormones, especially estrogens, reduce oxidative stress and account for women living longer than men. Brain cells with relatively lower turnover are subject to DNA damage with age [6]. It seems logical that female sex hormones that reduce oxidative stress might decrease the risk for Alzheimer's disease for women instead of increasing risk. Living longer, however, provides more opportunity for Alzheimer's disease to develop.

Finally, cognitive reserve is associated with education and use of brain in work [7]. Gender differences may only be associated with college education differences between men and women.

Thus, why women seem to have higher risk for Alzheimer's disease, is confusing, unknown, and contentious. Based on the many possibilities, there appears to be a need to better explain the effects of gender on Alzheimer's disease risk.

Gregory [1] presented a mathematical model that estimates the risk of developing Alzheimer's disease as a function of age. This model is based on the theory that waste products are flushed from the brain during slow-wave sleep. Unflushed amyloid β accumulates in the front executive part of the brain that also provides control over slow-wave sleep [8]. As people age, amyloid β accumulation weakens the control over slow-wave sleep causing less slow-wave sleep and less flushing.

Gregory [1] related slow-wave sleep to maximum oxygen uptake (VO_{2max}) that on average decreases with age [3] [4]. The mathematical model for VO_{2max} is the same for both men and women except for a gender factor currently estimated to be 10.5 ml·kg^{-1}·min^{-1} for men and 3.5 ml·kg^{-1}·min^{-1} for women. The current Alzheimer's model calibration is based on a mixed population of 50 - 50 men and women using an average gender factor of 7.0.

The gender effect on the prediction of Alzheimer's disease in the existing model is a consequence of using VO_{2max} to estimate the amount of daily slow-wave sleep [1]. For details on the prediction of slow-wave sleep, see Appendix B in Gregory [1]. The following equation is used in this process along with other equations described in his Appendix B [1]:

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

where VO_{2max} = maximum oxygen uptake (ml·kg^{-1}·min^{-1}).

RF = relative fitness (number between 0 and 1).

A = age (years).

G = gender factor (males: 10.5; females: 3.5) (ml·kg^{-1}·min^{-1}).

For details on the various relative fitness values and use of this equation to predict risks of fatal heart disease, probability of living, and time awake after sleep onset, see Gregory [9]. The relative fitness variable allows the model to consider fitness, a lifestyle choice, in predicting the risk of developing Alzheimer's disease as age increases. A value of 0.45 was used for relative fitness for a general population (1/4 endurance-trained ($RF = 0.67$) and 3/4 sedentary ($RF = 0.38$)) [9]. This value was used in the Alzheimer's model for a general population. Estimated risk for Alzheimer's disease is high for sedentary lifestyles compared to a physically active lifestyle as reported in the literature [10] [11]. The model seems to be on the right track in terms of physical lifestyles.

The gender factor allows the model to adjust predictions based on sex. When the model is run for a gender factor of 3.5 ml·kg^{-1}·min^{-1} for women and 10.5 ml·kg^{-1}·min^{-1} for men, it overpredicts the risk for women and underpredict the risk for men compared to the data from Lautenschlager *et al.* [12]. This built-in gender adjustment, nevertheless, relates back to a physical property of maximum oxygen uptake. The model appears to be missing additional gender factors.

Objectives

The objective of the current work is 1) to reassess the values used for male and female gender factors, 2) add gender related variables that change the risk of developing Alzheimer's disease based on published odds values reported in the literature, such as smoking and cognitive reserve, and 3) add a variable that adjusts the risk for developing Alzheimer's disease associated with hormonal changes of men and women as they progress through life (birth to death). A final objective is to add variables to the model to consider new medical understanding and treatments implemented after 1996 when Lautenschlager *et al.* [12] published their Alzheimer's disease risks as a function of age.

2. Methods

2.1. Step 1: Simple Gender Factor Adjustment

The simplest way to reduce the gender difference in the model is to adjust the gender factors to be closer to the neutral value of 7.0 as currently calibrated. The

current ratio of female to male predicted risk for lifetime (age 95) Alzheimer's disease risk is shown in red in **Figure 1**. A close match to the data from Lautenschlager *et al.* [12] is shown for a gender factor combination of 5.4 ml·kg^{-1}·min^{-1} and 8.6 ml·kg^{-1}·min^{-1} for females and males respectively. This ratio is shown as a green bar on the far right of **Figure 1**. A match for data from a more recent population study [2] is shown as the other green bars. The current model calibration overpredicts the ratio or difference between women and men for both data sets.

It should be noted that this more recent study [2] is based on data from the Framingham Heart Study and has much lower lifetime risk (about 1/5, 20 percent, for women, and 1/10, 10 percent, for men) than the risk from the MIRAGE study reported by Lautenschlager *et al.* [12]. Lautenschlager et al report a 43.9 percent lifetime risk for women and a 30.9 percent for men. These values are two to three times greater than the Framingham study. The differences between these two data sets are much greater than the gender factor problem analyzed in this paper. It appears that medical technology changed during the approximate 20-year timespan between the two studies. This difference will be addressed later in this paper.

The gender factor values of 5.4 ml·kg^{-1}·min^{-1} and 8.6 ml·kg^{-1}·min^{-1}, work reasonably well for predicting measured risk for predicting Alzheimer's disease over the lifespan of women and men for the data from Lautenschlager *et al.* [12]: R^2 = 0.99 for women and 0.97 for men. The values, however, are outside the range of acceptable values for the VO$_{2max}$ equations presented by Gregory [1] [9]. Thus, there is reason to suspect that other factors are gender dependent, such as sex hormones, smoking, and maybe others.

2.2. Step 2: Reanalyzing VO$_{2max}$ Data

The VO$_{2max}$ data reported by Tanaka *et al.* [3] for women was reevaluated with emphasis on the gender factor. The data has a linear pattern with an intersection
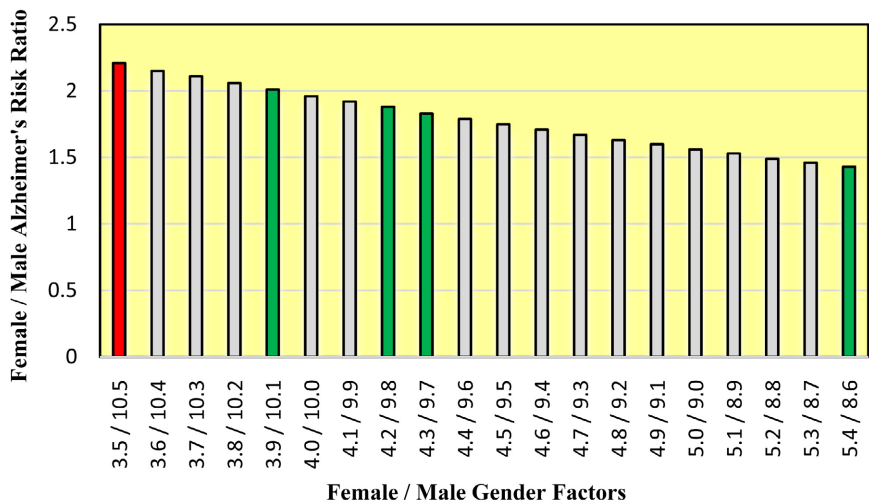

Figure 1. Illustration of the effect of changing the gender factors for females and males on predicted risk for lifetime Alzheimer's disease.

of the endurance trained group with the sedentary group occurring at age 120 years at or near the maximum lifespan for humans. The value at this common point is the gender factor for women. This value was varied and R^2 values determined for the linear model. The best R^2 value occurred with a gender factor of 3.5 ml·kg^{-1}·min^{-1} (R^2 = 0.858). The value of 5.4 ml·kg^{-1}·min^{-1} from Step 1 produced an R^2 value of 0.816 for comparison. Based on this comparison, the original value of 3.5 ml·kg^{-1}·min^{-1} is the best value for women and the proposed new value of 5.4 ml·kg^{-1}·min^{-1} was rejected.

A similar analysis was made for data for men reported by Pimentel *et al.* [4]. An R^2 of 0.775 resulted for the male gender factor of 10.5 ml·kg^{-1}·min^{-1}. The R^2 improved as the gender factor was lowered until a value of 9.5 ml·kg^{-1}·min^{-1} was obtained. This 9.5 ml·kg^{-1}·min^{-1} value resulted in an R^2 of 0.784. It is questionable whether this improvement in R^2 is sufficient to change the gender factor for men. Visually, the upper and lower relative fitness boundaries (See **Figure 2** in [9]) seemed to work slightly better with a gender factor of 10.5 ml·kg^{-1}·min^{-1}. The relative fitness values for boundaries as well as endurance-trained and sedentary data were all based on both the men and women data sets and were not changed for this current analysis. An R^2 = 0.782 was obtained for a gender factor of 8.6 ml·kg^{-1}·min^{-1}, but this value moved the upper boundary line below some of the extreme points. Considering both the R^2 values and the upper value for endurance-trained data, both 10.5 ml·kg^{-1}·min^{-1} and 9.5 ml·kg^{-1}·min^{-1} possibilities for the male gender factor were considered for the remaining analysis.

2.3. Step 3: Other Gender Related Factors

The main equation for the Alzheimer's model [1] is

$$R = \frac{365}{\beta_R}(1 - R_T)\sum_0^T \left(\beta_0 e^{-A_1 F_e S_{WF}}\right) \tag{2}$$

where R = risk of developing Alzheimer's disease expressed as fraction.

β_R = reference amount of amyloid β associated with onset of Alzheimer's disease.

R_T = accumulated risk expressed in previous year.

T = time in years.

β_0 = amyloid β production (calibration coefficient).

A_1 = calibration coefficient.

F_e = flushing system efficiency.

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

In the current model, the daily production rate is multiplied by 365 days. The Excel model works in yearly steps starting at zero and stopping after 120 years. A risk for each year is computed. The β amount after flushing (everything in the right parenthesis of Equation (2)) is added to the previous sum.

The summation expressed in Equation (2) times 365 is the total amount of amyloid β accumulated in the section of the brain that controls slow-wave sleep. This amount divided by β_R is the ratio of accumulated amount divided by the

amount that produces onset of Alzheimer's symptoms. This ratio can exceed one. The probability of developing Alzheimer's disease is limited to 1.0 by the component $(1 - R_T)$.

Two coefficients in Equation (2), β_0 and A_1, can be varied to change the calibration. Factors that change brain metabolism affect the production rate of amyloid β and affect the β_0 variable. Because β_0 cannot become negative, odds associated with variables cannot be additive leaving the next simplest model to be a product of odds or relative risk values.

Other factors, such as smoking and cognitive reserve, most likely affect A_1. Smoking affects oxygen and carbon monoxide in the lungs and blood [13]. Carbon monoxide and other chemicals in the blood should affect all brain cells nourished by the blood. Damage to the glial cells should reduce flushing during sleep.

The A_1 coefficient is embedded in the exponent of Equation (2) and should have a nonlinear relationship with odds. To deal with this problem, the Alzheimer's model was run with different values for A_1 (6.6 ± values) and the predicted risk value at 70 years of age was compared to the predicted amount for $A_1 = 6.6$. A calibration curve for A_1 was developed using this process. Results are shown in **Figure 2**. The following equation produced the line shown with the curve in **Figure 2**:

$$A_1 = 6.6 O_{dds}^{-0.39} \tag{3}$$
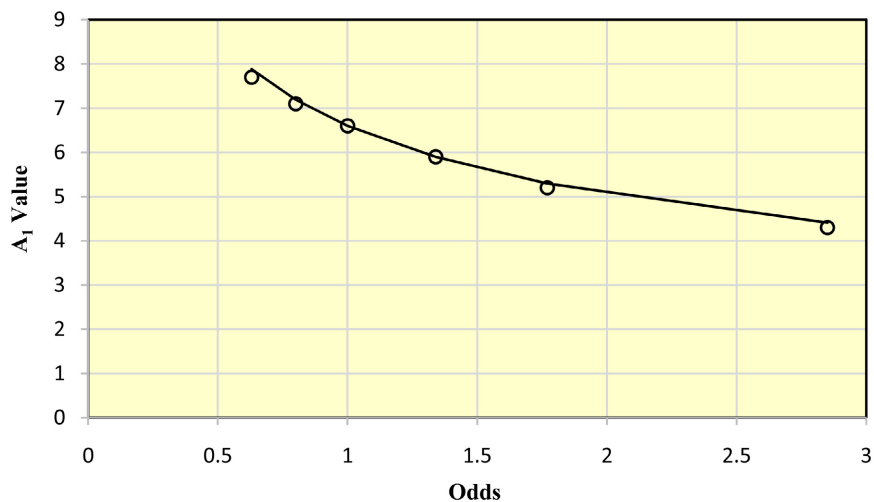
Figure 2. Calibration curve for coefficient A₁.

Populations are usually a mix of lifestyles unless experimentally controlled. For example, we would not expect 100 percent of the population in the MIRAGE Study [12] to smoke. Furthermore, men often have different lifestyle than women. The odds for considering a variable, such as smoking, must be adjusted based on the average choice of a lifestyle and for a difference in choice by gender.

The adjusted odds for a specific gender or mix of genders can be considered through Equation (4):

$$O_{ADJ} = \frac{\dfrac{G - \dfrac{G_M + G_F}{2}}{G_M - G_F}\left(\dfrac{M_\% - F_\%}{100}\right)C_O + \left[1 + \dfrac{M_\% + F_\%}{200}C_O\right]}{1 + \dfrac{M_\% + F_\%}{200}C_O} \tag{4}$$

where O_{ADJ} = adjusted odds for gender in a population.

G_M = male gender factor.

G_F = female gender factor.

$M_\%$ = percent of male population that has the lifestyle choice.

$F_\%$ = percent of female population that has the lifestyle choice.

C_O = change in odds (Odds from study minus one, ($C_O = O_{dds} - 1$)).

This somewhat messy equation can be view in simple terms. The calculation in the square brackets is the average odds for the lifestyle choice in the population. The calculation to the left of the square bracket in the numerator is a plus or minus adjustment for gender. If both genders have the same percentage of lifestyle choice, this term is zero. Historically, for example, a higher percentage of men than women smoked.

2.4. Smoking

Merchant *et al.* [14] evaluated the risk of smoking on developing Alzheimer's disease. They reported a relative risk for smoking of 1.9. If the original calibration had been performed for all nonsmokers, we would use an odds value of 1.9 to predict the risk for smokers. The population in the study did not exclude smokers. Thus, some smoking risk was embedded with other risks.

A difference in the prevalence in cigarette consumption by men and women [15] provides evidence for an interactive gender factor with smoking risk. **Figure 1** from Ng *et al.* [15] was used to estimate the percentage of women and men smokers for the period 1980 to 1995, the latter years associated with the MIRAGE Study. During this period, about 40 percent of men and 20 percent of women smoked. Thus, about 30 percent of the people in the MIRAGE study probably smoked.

The value for C_O in Equation (4) is Odds (1.9) minus one ($O_{dds} - 1 = 0.9$). An increase of 0.27 in risk in the data set probably occurred due to smoking (relative risk of 1.27; value in square brackets of Equation (4)). Men alone have a relative risk of 1.36 and women 1.19. The change in risk for women compared to 50 - 50 mix population is 0.929. For men, the change is 1.36/1.27, which is 1.071. Thus, there appears to be a gender interaction with smoking that affects the risk for Alzheimer's disease in the MIRAGE study population. The gender effect is approximately ± 7 percent.

The Excel model was expanded to include a column for smoking input including the percentages of men and women who smoked cigarettes. The adjustment was programmed to use the gender factor input and the two boundaries for gender (male gender factor and female gender factor) to facilitate the program to adjust for any mix of male and female input. If a zero is entered for both

the men and women smoking percentages, then the model predicts an adjusted odds of 1.0. If 100 percent is entered for both men and women, the model predicts an Odds adjustment of 1.9.

2.5. Cognitive Reserve

Dekhtyar *et al.* [16] defined cognitive reserve in terms of advanced education. They report an Odds of 0.63 for cognitive reserve compared to normal. The change in risk is 0.63 − 1.0 = −0.37. Next, the percentage of men and women who completed college at the time the MIRAGE study was made. Erin Duffin [17] reported in graphical form the percentage of US population with a college degree by gender from 1940 through 2021. The average percentage between 1970 to 1990 for men with a college degree is roughly 20 percent. For women, the value is roughly 14 percent. College and cognitive reserve were assumed to start at age 18 just after high school. The changes on total adjustment and A_1 are shown in Figure 3. It appears that cognitive reserve is only a minor factor in this population.

At present, the percentage of men and women with college degrees is about the same. Because cognitive reserve is directly related to advanced education, the idea that a smaller brain in women affects cognitive reserve as suggested by Chene *et al.* [2] seems to be false.

2.6. Sex Hormones

Vina *et al.* [5] report that women live longer on average by about eight years or about 10 percent compared to men. This difference is because females have less oxidative stress. They report that females live around 10 percent longer than males in many species. Furthermore, they conclude that the presence of estrogens affects the signaling up-regulation of antioxidant enzymes. Oxidative damage to mitochondrial DNA occurs in both the liver and brain as aging occurs. The "neuronal mitochondria produce much greater quantities of oxidants than do glial mitochondria" (Vina *et al.* [5] page 1361). This statement gives evidence that it is the neurons and not the glia or flushing system that is most affected by oxidants. Thus, the β_0 is the likely place to change the calibration for sex hormones. Furthermore, it has been shown [6] [18] that "apoptosis is enhanced in the frontal cortex, basal forebrain, and hippocampus of Fisher rats". These are the areas of the brain that are first affected by Alzheimer's disease.

It appears that gender might have two direct effects. One is through VO_{2max} that affects sleep for both men and women. The other is through differences in hormones. If female sex hormones decrease the risk of developing Alzheimer's disease in parallel with increasing longevity, then this effect would help explain why the current calibration of the Gregory Alzheimer's model overpredicts the risk of developing Alzheimer's disease for women.

Sex hormones for both women and men vary with age. Thus, the sex hormone calibration is expected to vary with age. Hormones appear to also vary with life

		Neurons: β_0 Changes					All Cell Types: Flushing			
		Enter 0, 1, 2	% Pop. Fat Treatment	% Pop.	% Pop.		Men %	20	20	
							Women %	14	20	
		0	0	0	100.0		Risk	-0.37	0.9	
		1.65	1.04	1.07	0.23		Pop. Risk	-0.0629	0.18	
Age	β_0	APOE4	Statin In	Viagra In	Sex Horm.	Rel. Δ	A_1	Educ.	Smoking	Total Adjust.
0	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
1	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
2	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
3	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
4	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
5	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
6	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
7	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
8	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
9	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
10	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
11	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
12	0.0325	1.00	0	0	0	1.00	6.60	1.00	1.00	1.00
13	0.0317	1.00	0	0	0.03	0.98	6.60	1.00	1.00	1.00
14	0.0312	1.00	0	0	0.05	0.96	6.60	1.00	1.00	1.00
15	0.0297	1.00	0	0	0.11	0.92	6.60	1.00	1.00	1.00
16	0.0245	1.00	0	0	0.32	0.75	6.60	1.00	1.00	1.00
17	0.0212	1.00	0	0	0.45	0.65	6.60	1.00	1.00	1.00
18	0.0180	1.00	0	0	0.58	0.55	6.60	1.00	1.00	1.00
19	0.0150	1.00	0	0	0.7	0.46	6.57	0.95	1.18	1.01
20	0.0120	1.00	0	0	0.82	0.37	6.57	0.95	1.18	1.01
21	0.0112	1.00	0	0	0.85	0.35	6.57	0.95	1.18	1.01
22	0.0105	1.00	0	0	0.88	0.32	6.57	0.95	1.18	1.01
23	0.0100	1.00	0	0	0.9	0.31	6.57	0.95	1.18	1.01
24	0.0095	1.00	0	0	0.92	0.29	6.57	0.95	1.18	1.01
25	0.0090	1.00	0	0	0.94	0.28	6.57	0.95	1.18	1.01
26	0.0087	1.00	0	0	0.95	0.27	6.57	0.95	1.18	1.01
27	0.0082	1.00	0	0	0.97	0.25	6.57	0.95	1.18	1.01
28	0.0080	1.00	0	0	0.98	0.25	6.57	0.95	1.18	1.01
29	0.0077	1.00	0	0	0.99	0.24	6.57	0.95	1.18	1.01
30	0.0075	1.00	0	0	1	0.23	6.57	0.95	1.18	1.01

Figure 3. Example Excel spreadsheet page showing smoking and cognitive reserve through college education on flushing (total adjustment) and β_0 adjustment based on sex hormones. Cells in yellow are calibration values.

events. Vina *et al.* [5] report that when ovariectomy is performed on women they have an increase in H_2O_2 production in both the liver and brain mitochondria. Furthermore, this increase results in values similar to men. Without ovaries, estrogen production is near zero. It appears that women have a unique design feature that protects the brain during childbearing years when they are more likely to lose sleep caring for babies and young children. They lose this advantage after menopause. On average, it appears that their aging is slowed, and lifespan is increased by about 10 percent during the premenopausal years.

Because the model was initially calibrated on a 50 - 50 mix of men and women, if there is a reduction in risk for women, then by default there should be an equal amount of increase in risk for men. If there is an increase in risk for men, then by default, there is a reduced risk for women. The following equation was formulated to estimate the relative risk associated with gender from sex hor-

mones:

$$S_{RR} = 1 - (1 - C_{SEX}) \frac{W_\%}{100} S_H + \left[(1 - C_{SEX}) \frac{100 - W_\%}{100} S_H \right] \quad (5)$$

where S_{RR} = relative risk due to gender from sex hormones

C_{SEX} = calibration coefficient between 0 and 1.0

$W_\%$ = women percentage

S_H = sex hormone factor that varies with age

Equation (5) produces an Odds of 1.0 when the population is a 50 - 50 mix. The value inside the square bracket goes to zero when the population is all women and the value for S_{RR} is less than 1.0. When the population is all men, the term to the left of the plus sign goes to zero and S_{RR} is larger than 1.0.

The Excel model was modified to change the calibration of β_0 as a product of the relative risk associated with sex hormone factors, S_H, as shown in **Figure 3** and **Table 1**. When a gender factor of 3.5 ml·kg⁻¹·min⁻¹ is entered (not shown in **Figure 3**), the percentage of women is shown as 100 percent. A 50 - 50 population for a neutral gender factor will produce a 50 percent women population. The value 0.23 in yellow in this column is the calibration value for C_{SEX} in Equation (5).

Values for the S_H variable were estimated by digitizing values of serum estradiol for women and serum testosterone for men from **Figure 1** of Decaroli and Rochira [16]. A relative value for women was generated by dividing the estradiol values by the maximum value of 180 pg/ml. Likewise, a relative value for men was generated by dividing the testosterone values by the maximum value of 620 pg/ml. Values are shown in **Table 1**.

Initially, only the relative value for estradiol was used. The C_{SEX} calibration coefficient was adjusted until a good R² value was obtain for the risk for women. This resulted in an under prediction for men. It appeared that predictions for women need to be reduced while increasing the predictions for men. The main problem seemed to occur after age 60. At this point male sex hormones dominate the S_H function. Thus, the average of relative sex hormone values for men and women was tried. A comparison of relative sex hormones is shown in **Figure 4**. Until about age 50 the relative values of male and female sex hormones seem to have about the same relative distribution with age.

The average of male and female relative sex hormones improved the model predictions. The C_{SEX} calibration coefficient was adjusted until predicted risk values for women closely matched the reported risk values for women from Lautenschlager *et al.* [12]. Ten points were obtained from their Figure B on page 645 to obtain 10 risk values for men and women at age 50 through 95. An R² of 0.99 was obtained when C_{SEX} was set to a value of 0.23. The results were highly significant (p = 0.001). A female gender factor of 3.5 ml·kg⁻¹·min⁻¹ was used. The predicted values did not change when a male gender factor of 10.5 ml·kg⁻¹·min⁻¹ or 9.5 ml·kg⁻¹·min⁻¹ was used in the calibration.

Table 1. Sex hormone values with age from Figure 1 of Decaroli and Rochira [16].

Women Serum E	Men Serum T	Age	Women Rel. E	Men Rel. T	Average
0	0	0	0.00	0.00	0.00
0	0	12	0.00	0.00	0.00
9	0	13	0.05	0.00	0.03
18	0	14	0.10	0.00	0.05
40	0	15	0.22	0.00	0.11
58	200	16	0.32	0.32	0.32
160	460	20	0.89	0.74	0.82
180	550	25	1.00	0.89	0.94
180	620	30	1.00	1.00	1.00
180	620	35	1.00	1.00	1.00
180	620	40	1.00	1.00	1.00
180	580	45	1.00	0.94	0.97
180	550	50	1.00	0.89	0.94
170	500	55	0.94	0.81	0.88
150	485	56	0.83	0.78	0.81
100	475	57	001	0.77	0.66
8	455	59	0.04	0.73	0.39
0	440	60	0.00	0.71	0.35
0	380	65	0.00	0.61	0.31
0	330	70	0.00	0.53	0.27
0	300	75	0.00	0.48	0.24
0	270	80	0.00	0.44	0.22
0	245	85	0.00	0.40	0.20
0	220	90	0.00	0.35	0.18
0	210	95	0.00	0.34	0.17
0	200	100	0.00	0.32	0.16

Next, the model was run at a gender factor of 10.5 for men with a calibration male gender factor of 10.5. The predicted values resulted in an R^2 equal to 0.993. A gender factor input of 9.5 with a male gender factor calibration of 9.5 ml·kg^{-1}·min^{-1} resulted in an R^2 equal to 0.997, but the predicted values overestimated the measured values by 20 percent. The slope of measured and predicted for this male calibration was 1.20. This result provided evidence against the use of 9.5 ml·kg^{-1}·min^{-1} as a male gender factor. A gender factor of 10 was then tried.
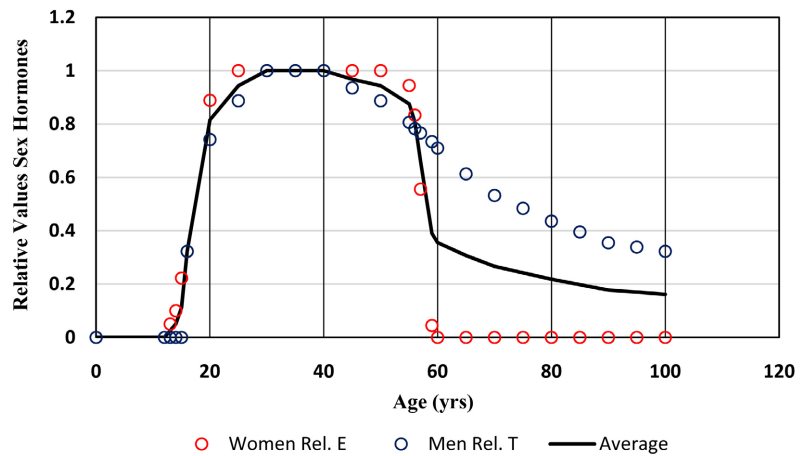
Figure 4. Comparison of relative values for male and female sex hormones. Original data from Decaroli and Rochira [16].

An R^2 equal to 0.995 resulted, but again the slope between measured and predicted was high at 1.10. On average, the use of a male gender factor of 10.0 ml·kg^{-1}·min^{-1} overpredicted measured values by 10 percent. Because the male gender factor of 10.5 ml·kg^{-1}·min^{-1} produced a slope of 1.00 between measured and predicted, it appears that this is the best gender factor to use for males in the model.

The predicted values for female gender factor of 3.5 ml·kg^{-1}·min^{-1} did not change with the three male gender factors tried. It was concluded at this point that the average of the relative sex hormone values from Table 1 was a reasonable way to adjust predictions for male and female genders.

By far, the sex hormone calibration adjustment had the most effect on the expanded calibration of the Gregory Alzheimer's model. With this adjustment, the model predictions closely matched both the male and female risks provided by Lautenschlager *et al.* [12]. Also, at this point it appears that the male gender factor of 10.5 is the best representation of males.

3. Results

Testing Model with Newer Data

Numerous references associate heart disease and Alzheimer's disease. Both seem to be related to saturated-fat intake and high levels of cholesterol [19] [20]. Management of diet and cholesterol-lowering treatments are important. Morris *et al.* [21] summarized the value of these two actions as follows:

> …studies have found that high-fat/high-cholesterol diets increased, and cholesterol-lowering drugs decreased amyloid β peptide deposition and Alzheimer disease-related abnormalities.

As mentioned earlier in this paper, the newer study reported by Chene *et al.* [2] has much less risk for Alzheimer's disease with age than the older study reported by Lautenschlager *et al.* [12]. Chene *et al.* [2] computed the risk for Alz-

heimer's disease with a process they defined as competing mortality. While their description of the process lacks detail, they considered the effect of early death from various causes on their final estimates of developing dementia and Alzheimer's disease, the major component of dementia. While their methodology is different from Lautenschlager *et al.* [12], the major differences between the two datasets appear to be due to improved medical knowledge and new treatments—not methodology.

A column was added to the Excel program to allow 0.0 or 1.0 as input at each year of age that statins are used. When statins or low-saturated fat diets are used, a 1.0 is entered. When statins are not used, a 0.0 is entered. The column was programed to produce a relative risk or odds ratio of 0.35 for each year statins are used based on the work of Wolozin *et al.* [20]. An entry of 0.0 produces an odds value equal to 1.0. The user also enters the percent of the population that manages their fat intake either through reducing saturated fat or taking cholesterol-lowering medicine.

Data from the US Department of Health and Human Services Center for Disease Control and Prevention (Kuklina *et al.* [19] was obtained from their **Figure 3** on the total percentage of people who met the guidelines for low saturated fat intake. Forty-two percent met the guidelines from 2001 through 2010. The prior period, 1988-1994, was only down by one percent at 41 percent. This left 58 percent with high fat and probably high cholesterol—a need for cholesterol-lowering medication. The same report gave the percentage of people using cholesterol-lowering medications as 39 percent. This resulted in 67 percent of the people needing cholesterol treatment receiving treatment.

The Alzheimer's model was then used to generate the lifetime risk (age 95) of developing Alzheimer's disease as shown in **Table 2**, specifically row for 67 percent receiving treatment. The smoking percentage for men was also reduced from 40 to 20 based on the data in the paper by Chene *et al.* [2]. Predictions for men varied with the value of male gender used in calibration: hence three columns of predictions are shown for men. Predictions for women did not vary with the calibration for men. Values for men over predicted the measured risk from Chene *et al.* [2]. Values for women were almost within the confidence range of measured values for the age 65 analysis (**Table 3**). In general, the model calibrated for 67 percent receiving treatment over predicted measured values. Chene *et al.* [2] also presented risk for dementia, which include the Alzheimer's disease risk.

Another way to consider the data reported by Kuklina *et al.* [19] is that 75 percent of the population in the US did not meet the guidelines for low saturated-fat intake in 1976-1980. Also, cholesterol-lowering drugs were just beginning to be used at this time. These condition probably closely reflect the condition in the population study reported by Lautenschlager *et al.* [12].

How people manage their fat intake certainly seems to affect risk in developing Alzheimer's disease. Morris *et al.*, [21] conclude the following:

Table 2. Predicted risk for Alzheimer's disease for men and women.

Population % Receiving Treatment	Men			Women
	Male Gender Factors			
	10.5 ml·kg⁻¹·min⁻¹	10 ml·kg⁻¹·min⁻¹	9.5 ml·kg⁻¹·min⁻¹	
100	0.102	0.112	0.121	0.165
90	0.114	0.124	0.135	0.192
85	0.121	0.131	0.143	0.192
85 (10% Viagra)	0.108	0.117	0.128	
85 (20% Viagra)	0.097	0.105	0.114	
80	0.127	0.139	0.151	0.202
75	0.135	0.147	0.159	0.217
75 (10% Viagra)	0.120	0.131	0.142	
75 (20% Viagra)	0.108	0.117	0.127	
70	0.142	0.155	0.168	0.229
67	0.147	0.160	0.174	0.235
67 (10% Viagra)	0.131	0.143	0.155	
67 (20% Viagra)	0.117	0.128	0.139	
0	0.314	0.340	0.365	0.446

Table 3. Lifetime risk for developing Alzheimer's disease from (Chene *et al.* [2]).

Analysis Description	Men %	Women %
Alzheimer's Disease: Competing Mortality-Adjusted starting at age 45	10.3 (8.9 - 11.8)	19.5 (17.8 - 21.2)
Alzheimer's Disease: Competing Mortality-Adjusted starting at age 65	11.6 (10.0 - 13.2)	21.1 (19.2 - 23.0)
Dementia: Competing Mortality-Adjusted starting at age 45	13.8 (12.2 - 15.3)	22.7 (20.9 - 24.5)
Dementia: Competing Mortality-Adjusted starting at age 65	15.5 (13.7 - 17.2)	24.6 (22.7 - 24.5)

High intake of unsaturated, unhydrogenated fats may be protective against Alzheimer disease, whereas intake of saturated or trans-unsaturated (hydrogenated) fats may increase risk.

Change in fat intake since the study used for calibration probably should be considered in the Fat Treatment column. In 2007-2010, 17 percent had lowered their saturated-fat intake plus 39 percent were on medications to lower cholesterol. The sum of 17 and 39 percent divided by the 75 percent needing to reduce

fat resulted in 56/75 or 74.7 percent achieved treatment for cholesterol. The predicted risk from the Alzheimer's model for a 75 percent achieving treatment is shown in the row for 75 percent treatment.

The prediction for women is close to the measured value for age 65 analysis (2.8 percent error). The predicted value of 13.5 percent for men for a male gender calibration of 10.5 is almost within the measured range for the age 65 analysis (Table 3).

There appears to be considerable scatter in the reported usage of cholesterol-lowering medications. Most values are below the 39 percent used above. In contrast, Franco [22] showed that cholesterol-lowering drug usage had increased from 23.4 percent of people 65 years and older to 46.8 percent by 2012. The sum of 17 for saturated fat reduction and 46.8 is 63.8 which results in 85.1 percent having treatment to lower saturated fat and cholesterol by 2012. The predictions in the row for 85 percent treatment is also shown in Table 2.

The predictions for both male gender factors of 10.5 ml·kg^{-1}·min^{-1} and 10.0 ml·kg^{-1}·min^{-1} were within the measured confidence range for the age 65 analysis. The predicted value for women is a close match to the measured value for age 45 analysis and within the range for the age 65 analysis.

There is uncertainty about the percentage of the people in the Framingham Heart Study in terms of unsaturated fat intake and usage of cholesterol-lowering medicines. The age 65 analysis started with older people who were less likely to have used cholesterol-lowering medications compared to the age 45 analysis. The measured data seem to reflect this change in usage of cholesterol-lowering drugs and use of better diets. The model seems to have done well in predicting the difference in age analysis and has done extremely well in predicting the reduction in risk for Alzheimer's disease from the older data set reported by Lautenschlager et al. [12]. For comparison, the predicted data for men and women with no treatment for high-fat diets for conditions in people living before 1996 [12] are shown in the bottom line in bold.

Finally, the model was run for 100 percent of the population managing their fat either through diet or cholesterol-lowering drugs. From this upper limit, it appears that further large reductions from cholesterol-lowering drugs are not very likely. A new drug development that reduces the odds below 0.35 is needs but probably unlikely.

These results favor the use of 10.5 for the male gender factor as was originally used in the Gregory model [1].

4. Discussion

Based on the expanded calibration for the Alzheimer's disease model presented by Gregory [1], it appears that several factors affect the gender difference in risk for Alzheimer's disease. Smoking, cognitive reserve, and sex hormones components were added to the model. It appears that the gender factor from the VO$_{2max}$ model and the sex hormone calibration are the two most important determi-

nates of the gender differences. Smoking and cognitive reserve differences in population studies have only a minor effect.

The gender factors for men and women were reanalyzed. There was little room statistically to deviate from the original gender factor of 3.5 ml·kg^{-1}·min^{-1} for women. When the gender factor of males was reanalyzed, it was found that a 9.5 ml·kg^{-1}·min^{-1} value produced the best R^2 value in the VO$_{2max}$ data. However, the difference between 10.5 ml·kg^{-1}·min^{-1} and 9.5 ml·kg^{-1}·min^{-1} was small. It now appears that the 10.5 ml·kg^{-1}·min^{-1} value for the male gender is the best value to use.

This paper started with the concern that the Gregory Alzheimer's disease model overpredicted risks for women. After adding components for sex hormones, smoking, and cognitive reserve, the model did well matching measured results reported by Lautenschlager et al. [12] for both women and men. The model did well in matching the results form Chene et al. [2] for women after adding a component to consider unsaturated fat diets and cholesterol medication, especially for women. The model slightly overpredicted the risks for men in this newer data set.

Why did this overprediction for men but not for women occur? The answer appears to be associated with another medication primarily used by men starting in the late 1990s—Viagra. Fang et al. [23] reported that an ED medication, Viagra (Sildenafil), reduced Alzheimer's development in men by 69 percent over a six-year period. They report a hazard ratio of 0.31, which was used in the expanded Gregory Alzheimer's model. While females had some benefit, their results were weaker. Females typically take a lower dosage and only a small percentage of women are prescribed this medication relative to men.

The percentage of men who took Viagra from 2000 to 2015 is unknown. The number is thought to be somewhat limited because of newness and cost. An assumed value of 10 percent was tried. The predicted results are shown in bold in Table 2 for 67, 75, and 85 percent of fat and cholesterol management. Even this small percent usage reduced the predicted risk for men to values close to measurements in Table 3.

Predictions for 10 percent usage in men were in line with measured values in Table 3 from Chene et al. [2]. Predictions for 20 percent usage in men are also shown in Table 2 and are a close match to the measured values in Table 3. While the actual population usage of Viagra in the data from Chene et al. [2] is unknown, it is logical that Viagra usage is the reason that the measured results for men in Table 3 were below the initial predictions without considering Viagra.

Adding Viagra as a treatment reduced the risk for men and raised the ratios for risk for women over risk for men. The ratio is approximately 1.77 for 10 percent Viagra and 1.97 for 20 percent. The ratios for the measured values are 1.82 for the 65-age group and 1.89 for the 45-age group. These measured ratios are approximately midway between the 10 and 20 percent usage values. While

the model does not predict the cause of Alzheimer's disease, it appears to correctly model the dynamics of the disease progression for both genders.

It appears that most of the gender factors have been included in the expanded model. There are probably gender differences associated with other risk factors, such as sleep apnea and obesity. Data to enable a reasonable calibration for these considerations were not found. Part of the problem, for example is that definitions of the number used to define sleep apnea vary. These two variables seem to be related and affect other health issues that often cause death before Alzheimer's disease has time to develop. Obviously, more research with precise measurements is needed.

5. Summary and Conclusions

Gregory [1] reported a mathematical model programmed in Excel to predict the risks of developing Alzheimer's disease and Chronic Traumatic Encephalopathy, CTE, as a function of age and other variables. This model considered gender through a gender factor of 10.5 ml·kg^{-1}·min^{-1} for males and 3.5 ml·kg^{-1}·min^{-1} for females. The initial model overpredicted the risks for women and underpredicted risks for men. Most of this problem was resolved by adding a sex hormone factor that varied with age. These calibration values were obtained by first obtaining values for estradiol for women from the literature as a function of age and dividing all values by the maximum value. This process provided a woman's relative hormone values (0 to 1) as a function of age. The process was repeated for male testosterone to obtain a man's relative hormone values. The average of these to relative values provided the sex hormone calibration values. Minor adjustments to predictions of risks associated with gender were made by considering gender differences in smoking history and cognitive reserve (education) history.

The expanded model performed well in estimating risks associated with gender compared to measured gender specific results reported by Lautenschlager *et al.* [12]. Values for R^2 comparing measured to predicted were 0.99 and were highly significant ($p = 0.001$).

A more recent data set (Chene *et al.* [2]) was used to consider the use of unsaturated fat diets and cholesterol reducing drugs for both men and women to reduce risk of developing Alzheimer's disease. Viagra for men to reduce risk of developing Alzheimer's disease was also considered. Final predictions for lifetime risk of developing Alzheimer's disease closely matched measured values and were certainly within the 95 percent confidence range of measured values for both genders.

While initially, it was thought that the male gender factor of 10.5 ml·kg^{-1}·min^{-1} might need to be adjusted, it now appears that the 10.5 ml·kg^{-1}·min^{-1} for men and 3.5 ml·kg^{-1}·min^{-1} for women are acceptable calibration values. These values worked well for both the older data set [12] and a newer data set [2] published about two decades later.

Finally, the expanded Gregory Alzheimer's model provides the same predictions for a 50 - 50 mix of males and females as the original model with the added feature that it now considers use of unsaturated fat diets, cholesterol reducing medications, and Viagra for men.

Conflicts of Interest

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

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