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Alzheimer's Disease: Modeling the Effect of Daily Steps

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Abstract

There is now clear evidence that exercise measured by step count per day can reduce the risk of developing dementia. A mathematical model is presented in this paper that predicts the reduction in risk for both men and women as a function of age, gender, and steps/day. The model is based on the theory that exercise increases slow-wave sleep, which in turn increases the flushing of waste materials from the brain, resulting in a reduced risk of developing dementia. Based on observed measured data, exercise as measured by daily step count has both a positive and a negative effect. The negative effect starts to dominate at high step counts. These two effects were mathematically modeled based on the assumption that exercise has a positive effect on slow-wave sleep by increasing cardiorespiratory fitness. It was also assumed that exercise increases aches, muscle pain, blisters, etc., which interfere with slow-wave sleep. While these assumptions were not verified directly, the model based on these assumptions was successful in predicting risks for dementia in association with daily step count. Simulations with the model matched measured data reported in the literature with high R^2 values and statistical significance.

Keywords

Daily Steps, Exercise, Cardiorespiratory Fitness, Dementia, Alzheimer's Disease, Endurance Training, Slow Wave Sleep, VO_{2Max}

1. Introduction

Ding *et al.* [1] provided results from a meta-analysis relating risks for various health issues to daily steps. One of these health outcomes was dementia, the focus of this paper. Pooling data from the literature, they observed a general non-linear decline in risks for dementia as step count increases to about 9000 to 10,000 steps per day. After the minimum point is reached, the risks begin to increase as step count increases. The pooled data provide a trend for dementia risks as a function of daily steps, but the authors did not speculate on how or what factors might contribute to this relationship.

Nguyen *et al.* [2] reported a similar data set for women. They suggested that several biological mechanisms could explain their results, including cardiorespiratory fitness, which is associated with lower white matter lesions and larger brain volume. Beyond these two physical components in the brain, they did not offer an explanation of how the process might work. Also, they did not offer an explanation for why there would be an increase in risks as steps and presumably cardiorespiratory fitness continue to increase. The two datasets presented for women only also do not match the general relationship provided by Ding *et al.* [1]. Endurance training exercise seems to reduce the risk of developing dementia, especially in older women, more than the relationship provided by Ding *et al.* [1].

The objective of this paper is to present a mathematical model that considers sleep quality and the flushing of toxic waste as a possible process for predicting the observed measured outcomes.

2. Methods

As people age, there is generally a loss in mental function, especially memory. Dementia is an early-onset and severe form of these symptoms. The most common form of dementia is Alzheimer's disease, accounting for 60 to 80 percent of dementia cases. This paper will focus on the process of developing Alzheimer's disease and daily steps as a measure of physical activity. Daily steps fail to measure the intensity of exercise, but a low step count is an indication of inactivity. Tudor-Locke *et al.* [3] have successfully related step count to general physical fitness activity (basal activity, limited activity, low activity, somewhat active, active, and highly active). Ding *et al.* [1], Nguyen [2], and del Pozo Cruz *et al.* [4] have successfully used daily step count to estimate the risk of developing dementia. Nevertheless, daily step count is only an indirect proxy for aerobic fitness as measured in terms of VO_{2max}, the accepted standard for measuring cardiorespiratory fitness.

This analysis will test the cardiorespiratory fitness component (relative fitness) used in a mathematical model that simulates the risk of developing Alzheimer's disease [5] [6]. Alzheimer's disease is associated with the buildup of amyloid β and tau waste products that, when not flushed properly, accumulate in the brain. This buildup interferes with memory (hippocampus), executive function (frontal lobe), and the regulation of sleep [7]. Walker [7] provides a detailed description of the theory behind this process, relating it to both sleep and brain functions. This process is probably not the cause of Alzheimer's disease, but it seems to affect the rate of progression. The model presented in this paper should not be viewed as a cause of Alzheimer's or the more general term of dementia. The model should only be viewed as an empirical management tool using daily steps as a simple assessment of physical activity. The predictions from the model seem to support the theory of Walker [7].

The following steps will be used in this development:

1. Relationship between relative fitness and daily step count.
2. Review of the flushing components in the Gregory Alzheimer's model.
3. Application and testing of a mathematical model compared to published data.

2.1. Step Count and Relative Fitness

The Alzheimer's disease model by Gregory [5] [6] uses a relative fitness factor that is independent of age and gender. It considers fitness associated with aerobic exercise. The relative fitness variable is the slope in a linear model that predicts $VO_{2\max}$ as a function of age based on measured data (**Figure 1**) for women [8] and a similar relationship for men [9]. This model is discussed in detail by Gregory [10].

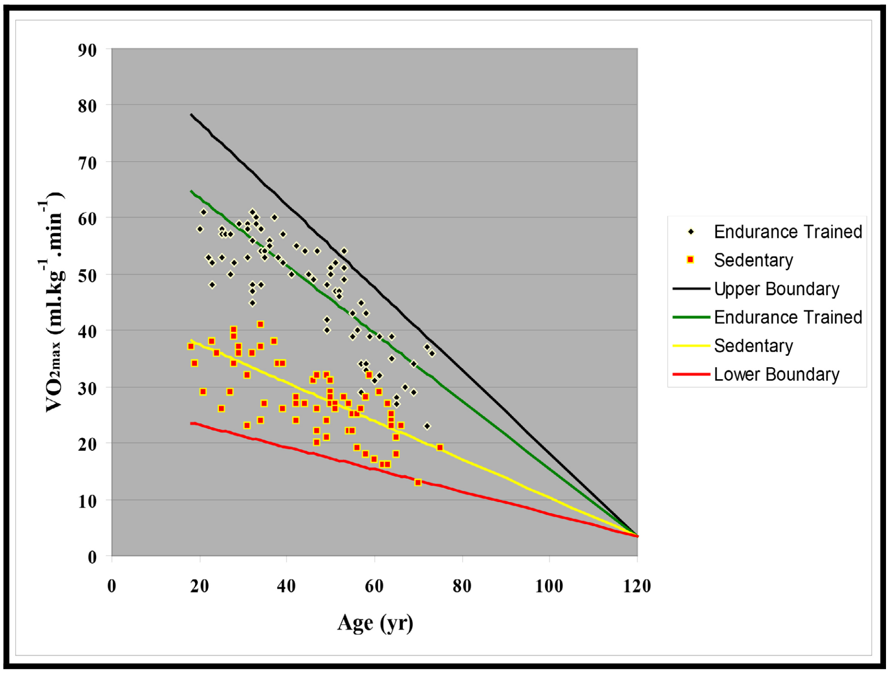

Figure 1. Reduction of $VO_{2\max}$ for women as a function of aging and fitness lifestyle. Data from Tanaka *et al.* [8].

The linear relationship shown in **Figure 1** is described by the following equation:

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

where $VO_{2\max}$ = aerobic fitness (ml•kg^{-1}•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 (¼ endurance trained & ¾ sedentary)
- (0.38) sedentary
- (0.20) approximate lower limit for sedentary
- (0.00) non active bed rest

A = age (years)

G = gender coefficient (males: 10.5; females: 3.5) $\text{ml}\bullet\text{kg}^{-1}\bullet\text{min}^{-1}$

The relationship works for both men and women. Relative fitness is a measure of lifestyle choice. The yellow line, for example, in **Figure 1** has a slope, or relative fitness, of 0.38, an average of the measured data for this sedentary group. The average for the two relative fitness sedentary boundaries (0.20 and 0.50) is 0.35, close to the average of 0.38. An estimate of the average relative fitness for the lower one-half of the sedentary classification is [(0.2 + 0.35)/2] 0.28. The average of the upper one-half of the sedentary classification is [(0.35 + 0.5)/2] 0.43. The average relative fitness for endurance training is 0.67. The halfway value between the two endurance training boundaries is 0.66 (close to the average of 0.67 for endurance-trained people). Following the same procedure as with the sedentary classification, the average of the lower half is 0.58 and the upper half is 0.74. These values are based on measured VO_{2max} and age data from [8] [9]. The variable, VO_{2max}, is often considered the gold standard for measuring cardiorespiratory fitness.

A parallel classification of steps/day and physical activity is provided by Tudor-Locke *et al.* [3]. Less than 2500 steps/day is labeled basal activity. Values between 2500 and 4999 are classified as limited activity. The combination of these two groups is considered sedentary. Values between 5000 and 7499 are considered low activity. Values from 7500 to 9999 are considered somewhat active. Active is defined as between 10,000 and 12,499. Finally, values larger than 12,500 are considered highly active.

The relationship between step count and relative fitness appears to be non-linear for both the effects of steps/day and age. Tudor-Locke *et al.* [3] [11] report that boys should get 12,000 to 16,000 steps/day and girls 10,000 to 13,000 steps/day. They also report that adolescent boys and girls get 10,000 to 11,700 steps/day.

Equation 2 was developed based on the logic that there is a diminishing return in terms of relative fitness as steps/day increase, with an upper limit for endurance-trained people near 0.82. The data indicating that children need more steps/day to obtain the same relative fitness requires an age variable in the mathematical model. There is also a lower relative fitness of about 0.2, as observed in **Figure 1**. The observation that the spread between the lower and upper boundaries for relative fitness in **Figure 1** implies that young people need more exercise to obtain the same relative fitness. Equation 2 was formulated to consider these variables:

$$RF = 0.45\left(1 - e^{-0.000082(Steps=1000)}\right)A^{0.11} + 0.2 \tag{2}$$

where $Steps = steps/\text{day}$

Equation 2 is an empirical estimate of relative fitness from VO_{2max} measurements as shown in **Figure 1**. The relative fitness values in **Table 1** are predicted with

Equation 2 for adults (age 20-100). The basal activity group from Tudor-Locke *et al.* [3] apply to the first two rows for steps 1000 and 2000. The next group, Limited activity, is for steps 3000 and 4000. The next group (low activity) is for steps 5000 to 7000. The somewhat active group applies to steps 8000 to 9000. The 8219 steps per day results in 3 million steps per year. The active group applies to steps 10,000 to 12,000 and the highly active group applies to steps above 13,000 steps per day. Relative fitness (0.28) defined as low sedentary is shown in the VO_{2max} column. The relative fitness associated with steps/day for lower sedentary [3] is shown in the TL column and was computed by averaging all value in the sedentary groups. The other relative fitness groups were averaged the same way for each Tudor-Locke *et al.* [3] groups.

Table 1. Predictions of relative fitness as a function of steps per day and age.

Steps	Relative Fitness						Tudor-Locke *et al.* (2011)	VO_{2max}	TL
	Age = 8	Age = 15	Age = 30	Age = 60	Age = 80	Age = 100			
1000	0.20	0.20	0.20	0.20	0.20	0.20	Basal Activity	0.20	0.20
2000	0.24	0.25	0.25	0.26	0.26	0.26			
3000	0.29	0.29	0.30	0.31	0.31	0.31	Limited Activity	0.28	0.28
4000	0.32	0.33	0.34	0.35	0.36	0.36			
5000	0.36	0.37	0.38	0.40	0.40	0.41	Low Activity		
6000	0.39	0.40	0.42	0.44	0.45	0.45		0.43	0.44
7000	0.42	0.44	0.45	0.47	0.48	0.49			
8000	0.45	0.46	0.49	0.51	0.52	0.53	Somewhat Active	0.50	0.51
8219	0.45	0.47	0.49	0.52	0.53	0.53			
8500	0.46	0.48	0.50	0.52	0.53	**0.54**			
9000	0.47	0.49	0.51	**0.54**	**0.55**	**0.56**		0.58	0.55
1,0000	0.50	0.52	**0.54**	**0.57**	0.58	0.59	Active		
11,000	0.52	**0.54**	**0.57**	0.60	0.61	0.62			
12,000	0.54	**0.56**	0.59	0.62	0.63	0.64			
13,000	**0.55**	0.58	0.61	0.64	0.66	0.67	Highly Active		
14,000	0.57	0.60	0.63	0.66	0.68	0.69			
15,000	0.59	0.61	0.65	0.68	0.70	0.71			
16,000	0.60	0.63	0.66	0.70	0.72	0.73			
17,000	0.61	0.64	0.68	0.72	0.73	0.75			
18,000	0.63	0.66	0.69	0.73	0.75	0.76		0.74	0.74
19,000	0.64	0.67	0.70	0.74	0.76	0.78			
20,000	0.65	0.68	0.72	0.76	0.78	0.79			
21,000	0.66	0.69	0.73	0.77	0.79	0.80			
22,000	0.66	0.70	0.74	0.78	0.80	0.81			
23,000	0.67	0.71	0.75	0.79	0.81	0.82			
24,000	0.68	0.71	0.75	0.80	0.82	0.83			
25,000	0.69	0.72	0.76	0.81	0.83	0.84			

There is a close match between relative fitness defined from **Figure 1** (VO_{2max} column) and predicted relative fitness based on steps/day classifications by Tudor-Locke *et al.* [3] (TL column). The predicted relative fitness of 0.55 associated with 13,000 steps/day for boys and girls is about the same as the relative fitness associated with 9000 to 10,000 steps/day for adults. The R^2 between the VO_{2max} column and the TL column is 0.998, which is statistically significant ($p < 0.001$) using Student's t-test.

Values from Equation 2 never exceed the upper boundary of relative fitness of 1.0. The upper value of 25,000 steps is approximately 10 to 11 miles in distance, depending on a person's height and age. Thus, the upper value of 25,000 steps in **Table 1** is a reasonable upper limit for most people. A few people, such as marathon runners or walkers, will exceed 50,000 steps per day or even 100,000 for double marathon runners. Even at these extreme values, predictions from Equation 2 do not exceed a relative fitness level of 1.0.

An extreme example of the effects of aerobic exercise on sleep, especially slow-wave sleep, was reported by Shapiro *et al.* [12]. They found that men, aged 22 years, more than doubled their slow-wave sleep component during the first two nights after completing a double marathon. The elevated slow-wave sleep followed an exponential decay function during days 2, 3, and 4. Projecting this function back to day 1, it is estimated that there was about a 25 percent reduction in the potential slow-wave sleep component due to the immediate effects of exercise on sleep quality, as evidenced by increased time awake after sleep onset and elevated stage 1. The authors suggested that the men suffered from muscle pain and blisters. After four days of recovery, sleep returned to normal. Exercise, thus, has two possible effects: an increase in slow-wave sleep and an increase in the potential for muscle aches and pain, which may reduce slow-wave sleep.

2.2. Flushing Model

The Alzheimer's model developed by Gregory [5] has a flushing function that depends on predicted slow-wave sleep. Several equations define this flushing component in the model.

Sleep is a cyclic process. As a person ages, they usually experience fewer cycles and less total sleep compared to young adults. The following equation is used to estimate the number of cycles, N_T, experienced per night:

$$N_T = 5.26 - 0.0212A \tag{3}$$

A 90-minute length is assumed for each cycle.

The value for N_T is used in Equation 4 to estimate the total time of slow-wave sleep that occurs per night of sleep:

$$S_{WT} = \frac{d_1}{d_2}\left(1 - e^{-d_2 N_T}\right) \tag{4}$$

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

d_1 = calibration variable computed from Equation 5

d_2 = decay rate (1.1)

$$d_1 = 0.0000168 VO_{2max}^3 \tag{5}$$

The variable $VO_{2\max}$ is computed using Equation 1.

All of these steps are used to estimate the amount of amyloid β left in the brain after flushing, as predicted by Equation 6:

$$W_F = W_0 \, e^{\wedge - A_1 F_e S_{WT}} \tag{6}$$

where W_F = waste products remaining in the brain

W_0 = waste production

A_1 = calibration coefficient (6.6)

F_e = flushing system efficiency (1.0)

The variable F_e is generally 1.0 or close to 1.0. It decreases when a person is repeatedly exposed to head trauma, such as that experienced by football and soccer players [5].

Equation 6 estimates the waste material that accumulates in the brain each day. It is impractical to enter data for each day. Thus, the W_0 value is multiplied by 365 days per year to obtain an accumulation for each year. The model then sums the amount for each year to get a total accumulation as a function of age. Because Equations 1, 2, and 3 include age as a variable, W_F varies with age. Gender is included through Equation 1.

Because slow-wave sleep decreases with age, the waste product remaining in the brain, W_F, increases each year. Thus, while waste products accumulate throughout life, the accumulation is greatly increased during middle and older ages.

The waste production is estimated from other components in the model that affect amyloid β production, such as APOE4, diet, use of statins, use of Viagra for males, consumption of eggs, cognitive reserve, smoking status, and sex hormones [5] [6].

Cardiorespiratory fitness is considered through relative fitness and the gender factor in Equation 1. The next section will use this flushing model and Equation 2 to estimate relative fitness to test and modify the risk of developing Alzheimer's disease as a function of daily steps.

3. Results

Four datasets were used to evaluate the effect of steps/day on the risk of developing Alzheimer's disease. One by Ding *et al.* [1] is a summary from a meta-analysis. The other three, by del Pezo Cruz *et al.* [4] and Nguyen *et al.* [2], are individual studies rather than meta-analyses. Each study has value. All four studies (two by Nguyen *et al.* [2]) observed a reduction in the risk for dementia as exercise increases. All three datasets express a relative risk of dementia with slightly different reference (steps/day) values. The datasets published by Nguyen *et al.* [2] have data starting at approximately 1250 steps/day. This value is classified as basal activity [3] and may represent an excessively elevated risk for dementia because of both low steps/day and probably a slow rate of movement (low intensity of exercise).

An alternative reference step count will be used for this dataset, as discussed later.

The Alzheimer's model was calibrated from Alzheimer's disease data. The four data sets used in this paper relating risk to daily step count are for all types of dementia. Because 60 to 80 percent of dementia is due to Alzheimer's disease, the four datasets for dementia were assumed to be sufficiently related to Alzheimer's disease to test and adjust the calibration of the Alzheimer's model.

One basic rule in developing a mathematical model is to look at the data before model development. Four datasets relating to the risk of developing dementia are shown in **Figure 2**. The points shown in red from Ding *et al.* [1] are a summary or meta-analysis. The other datasets are individual studies. First, note that all datasets have roughly the same shape. The two datasets from Nguyen *et al.* [2] are shifted down from the other two datasets. The data from Nguyen *et al.* [2] are for women only and may be shifted because of gender. Data from del Pozo Cruz *et al.* [4] appears to be the most complete of the studies: smooth over a wide range of step counts. Data from Ding *et al.* [1] is a meta-analysis and is a relatively close match both in shape and numeric values compared to the del Pozo Cruz *et al.* [4] data.

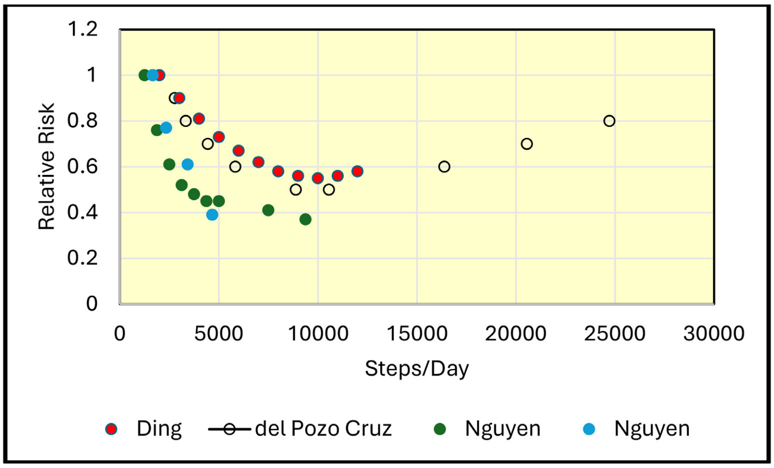

Figure 2. Measured relative risk for dementia from four data sets (Ding *et al.*, [1]; del Pozo Cruz *et al.*, [4]; Nguyen *et al.*, [2]). The slight shift (left/right) at a relative risk of 1.0 is due to the shift in reference step count.

There appear to be two functions affecting the shape of the del Pozo Cruz [4] data. A linear function appears to describe the relationship at high step values. This function also appears to be the lower boundary for an exponential decay function decaying down to the lower limit as step count increases. These two functions can be added together to describe the data in **Figure 3**. The data illustrated with blue dots do not appear to follow the general pattern. They are for 84-year-old women only.

None of these researchers speculated on how step count might affect processes in the brain. One possibility is that these two functions relate to the flushing of waste materials from the brain during slow-wave sleep. The linear increase in dementia risk as step count increases could be associated with an increased probability of aching muscles, joints, and blisters, causing decreased sleep quality as exercise increases. The exponential decline in risk for dementia might also be an issue with sleep quality. As aerobic exercise decreases, the time awake after sleep onset increases [13], causing less sleep efficiency.

Based on the observation and theory that a linear function might be involved in reducing the benefit of exercise, a linear adjustment to predicted slow-wave sleep was attempted. A linear function worked well but produced a high relative risk when a gender factor for men (10.5) was used. The linear model was adjusted to a square root function to reduce the growth in the loss of benefit as large step counts occur. The following adjustment to the sleep function is proposed:

$$S_{WT\,new} = S_{WT}\left(1 - C_1 RF^{C_2}\right) \tag{7}$$

where $S_{WT\,new}$ = new slow-wave sleep amount

C_1 = calibration coefficient (1.08)

C_2 = calibration coefficient (0.5)

These calibration values for C_1 and C_2 are for all four datasets.

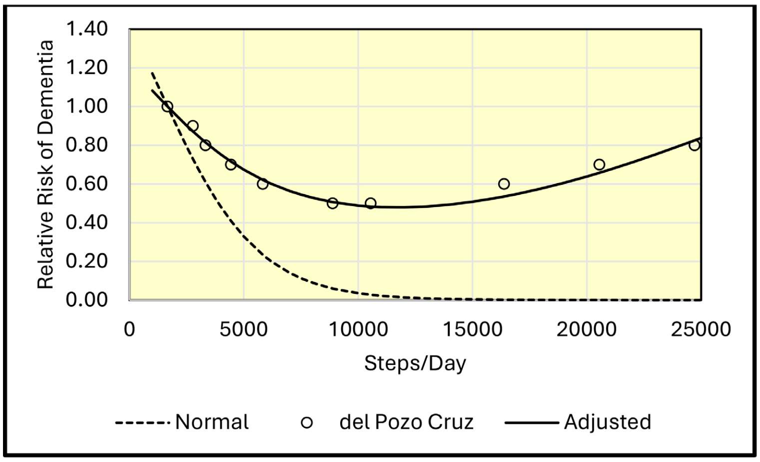

Figure 3. Comparison of measured and predicted (adjusted) relative risk for dementia. Data from del Pozo Cruz [4]. The dashed line (normal) is predicted from the model without adjustment from Equation 7. Data are for a mixed population of men and women.

Using sleep as the only adjustment from exercise was not sufficient to model the last dataset (blue dots in **Figure 2**). According to Equation 6, waste materials in the brain can be affected by both the production of waste and the flushing of waste. An adjustment to the production, W_0, in Equation 6, described later, was used with Equation 7. This adjustment is 1.0 or very close to 1.0 except for low VO_{2max} values that typically occur only for older women (age and gender effect).

The new predicted slow-wave sleep was then used in Equation 6 to calculate the waste products remaining in the brain. The waste predictions from the model were then divided by the waste prediction associated with the reference step count for each dataset to obtain the relative risk associated with each dataset.

For the del Pozo Cruz [4] dataset, the reference number of steps was 1667. The average age at the beginning of the study (61.1 years) plus one-half of the length of the study (3.5 years) resulted in an average age of 64.6 years during the study. Also, a gender factor of 6.57 was used based on the fraction of men and women in the study population. There is no age or gender variable in Equation 7. However, age and gender are used in the flushing model to predict S_{WT}. The above equation and calibration resulted in an R^2 of 0.971 for all 10 points in the dataset ($p < 0.001$). The other datasets only include data for 12,000 steps or fewer per day. Restricting the data to only data less than 12,000 steps reduced the measured data to only seven points. However, the R^2 increased to 0.977 ($p < 0.001$). These results are shown in Figure 3. Unadjusted predictions from the flushing model are shown as a dashed line. As seen in the dashed line, the decay component seen in Figure 3 was provided by the existing slow-wave sleep/exercise component in the Alzheimer's risk model [5]. The dashed line also indicates that the Gregory Alzheimer's model overestimates the benefit of exercise, neglecting the assumed negative feedback effect on slow-wave sleep due to aches and pain from exercise.

This model was also tested for all males (gender factor = 10.5), as shown in Figure 4. These predicted results show a reduced advantage for steps above 20,000. These changes, however, are within the 95 percent confidence range for a mixed population reported by del Pozo Cruz *et al.* [4]. At the other boundary condition (females, gender factor = 3.5), the opposite result occurred, also within the 95 percent confidence range.

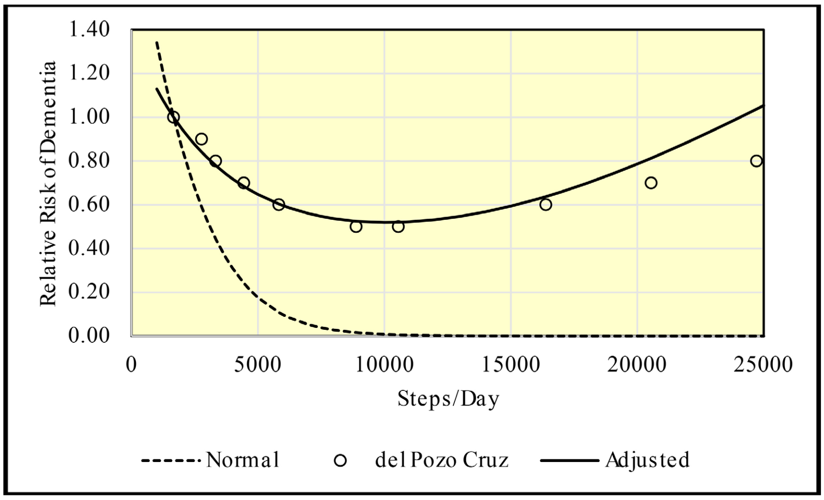

Figure 4. Comparison of measured and predicted (adjusted) relative risk for dementia for men only. Data for the mixed population are from del Pozo Cruz [4]. The dashed line (Normal) is for predictions from the model without adjustment from Equation 7.

A boundary condition check was tested next. At age 20 years (young adult), the adjusted and normal functions are almost the same, and the relative risk of dementia is low. At age 120 years, the adjusted risk is 1.0 for all levels of exercise, as expected from Figure 1 when all relative fitness slopes converge to a point at age 120 years. Because all relative fitness lines converge together at this age, there is no opportunity for exercise to reduce risk.

Data from Ding *et al.* [1] were used next. The authors did not provide an age or gender for this dataset. A gender factor of 7.0 (average of 10.5 and 3.5) was assumed. A 68-year-old age provided the best result: $R^2 = 0.982$ ($p < 0.001$). The results are shown in **Figure 5**. The upper and lower values for the 95 percent confidence interval are also shown.

Because the data presented by Ding *et al.* [1] are from a meta-analysis, these results are probably the most general. The range in daily steps, however, is limited to 12,000. The mathematical model seems to work well for both datasets evaluated at this point.

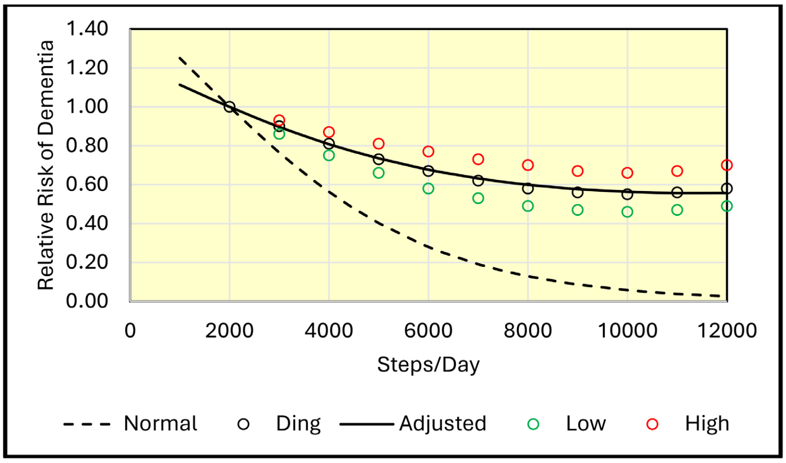

Figure 5. Measured and predicted (adjusted) risk of dementia from a meta-analysis. Measured data from Ding *et al.* [1]. The dashed line (Normal) is for predictions from the model without adjustment from Equation 7.

A third dataset [2] restricted to women only (gender factor = 3.5) was used to test the model next. The age at the start of the study was estimated by averaging the beginning and end of the age range and then adding 2.0 years because the exercise component started two years after the original study. The follow-up period was 4.2 years, resulting in an estimated average age of 68.6 years. This dataset and its predictions are shown in **Figure 6**.

There appears to be an anomaly in this dataset associated with the first data point. The number of steps for the first point is in the basal range and may be associated with both a low step count and a slow pace at which the exercise was performed. The second point was used as a reference, which resulted in an $R^2 = 0.946$ ($p < 0.001$) not including the first point shown in red. This dataset illustrates the importance of selecting a reference point that is part of the general trend line.

The last dataset considered had the fewest number of points and was the most difficult to model. Equation 7, as calibrated for the other three datasets, failed to predict the measured results reported by Nguyen *et al.* [2] for older women.

The second dataset by Nguyen *et al.* [2] is different from the first dataset. Both are for women only. The only obvious difference is that the second dataset is for older women with an average age of 84.1 years compared to the younger women with an average age of 68.6. The model failed to predict these reported results when an age of 84.1 years was used as an input.

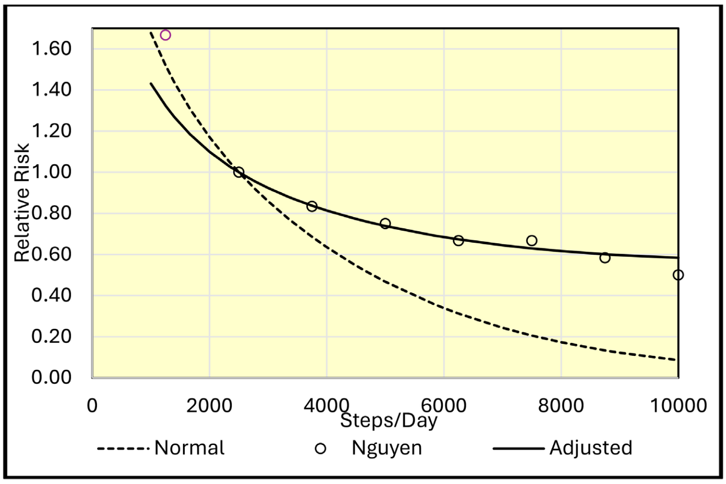

Figure 6. Predicted (Adjusted) and measured risk for dementia for 68.6-year-old women. Data from Nguyen *et al.* [2]. The dashed line (Normal) is for predictions from the model without adjustment from Equation 7.

The data for old women as illustrated in **Figure 2** (blue dots) does not follow the general pattern of the other three datasets. The data decline at a much steeper slope without much curvature as the number of steps increases. Assuming that the data are valid, there must be something overlooked in the model related to age.

In the Alzheimer's model developed by Gregory [5] [6], the W_0 in Equation 6 is adjusted by a product of odds ratios or relative risks reported in the literature, such as the use of statins to reduce cholesterol, the use of Virgia by men, the consumption of eggs, and other treatments or risk factors. Halverstadt *et al.* [14] found that endurance exercise reduces total cholesterol, triglycerides, and low-density lipoprotein cholesterol in older men and women. It appears that the source of cholesterol and other metabolic factors that lead to an increased risk for dementia are affected by exercise as well as by the flushing process related to sleep.

Hagner *et al.* [15] studied changes in VO_{2max}, blood lipids, and waist circumference as a function of moderate endurance training. They observed a significant difference in VO_{2max} and cholesterol as a function of age. Other measures, including BMI, total fat mass, low-density lipoprotein, high-density lipoprotein, triglycerides, and waist circumference, had insignificant changes associated with age. These variables all declined in association with endurance training, except high-density lipoprotein, which increased. Because these metabolic measures changed in association with endurance training and not age, it is reasonable that the age effect for cholesterol was through the age effect on VO_{2max}.

The probability of living decreases as age increases, but the function is highly sensitive to changes in VO_{2max} [13]. Gregory [13] used the inverse of VO_{2max} cubed to predict the probability of living associated with age and exercise. We have already used the cube of VO_{2max} to predict the amount of slow-wave sleep.

The following adjustment factor to W_0 was tried based on the assumption that VO_{2max} becomes very low with both aging and lack of exercise, especially for women (gender factor 3.5), leading to an increase in W_0:

$$W_{0A} = \left(1 + \frac{z}{VO_{2max}{}^3}\right) \tag{8}$$

where W_{0A} = adjustment to W_0 in Equation 6

z = calibration coefficient (1600)

The calibration coefficient, z, was determined using the data provided by Nguyen *et al.* [2]. Results for this dataset are shown in **Figure 7**. The predicted curve (solid line) resulted in an R^2 equal to 0.867 ($p < 0.05$).

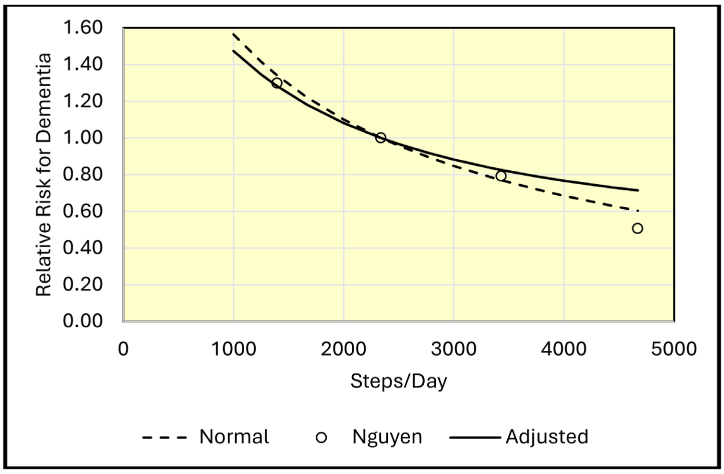

Figure 7. Predicted (Adjusted) and measured risk for dementia for 84.1-year-old women. Data from Nguyen *et al.* [2]. The dashed line (Normal) is for predictions from the model without adjustment from Equation 7.

The adjustment expressed in Equation 8 has very little effect on the predictions for the other datasets because the adjustment rapidly approaches 1.0 as VO_{2max} increases with younger ages. There was not a man-only dataset, but because men have a gender factor of 10.5 compared to women with a gender factor of 3.5, the VO_{2max} values for men should be high enough to produce a value for W_{0A} close to 1.0 for all ages.

Note that the dashed line from the unadjusted (Normal) Alzheimer's model [5] [6] closely matches these data for older women.

4. Discussion

Ding *et al.* [1] provided a relationship between the risk for dementia as a function of physical activity measured by steps/day. This function is smooth and continuous, providing the risk for dementia from 2000 steps/day through 12,000 steps/day.

They also provide a 95 percent confidence interval, providing statistical bounds on the relationship. Their relationship (**Figure 5**) shows an inverse relationship, declining in risk until about 9500 steps/day. Between 7000 and 8000 steps/day, a 40 percent reduction in risk is observed. Their results are from a meta-analysis of a literature review of several research papers. It seems to be an average effect. They, however, did not consider associations with age, gender, or step counts higher than 12,000.

Three other datasets are shown in **Figure 2**. One study for a mix of men and women with an average age of about 65 years is relatively close in both magnitude and shape to the data from Ding *et al.* [1]. These results are shown in **Figure 2** as red and open black data points. Data from middle-aged women and women aged 84 years show considerable differences from the data of Ding *et al.* [1]. Women, especially older women, seem to be more responsive to small amounts of exercise. The data from Ding *et al.* [1] underestimate the value of exercise in reducing the risk of dementia for these women.

No explanation of how exercise reduces the risk for dementia, other than the effects of cardiorespiratory fitness on the aging brain, was provided for any of the datasets. Walker [5] identified one process related to exercise: the flushing of waste products from the brain during slow-wave sleep. Gregory [5] built on this theory to develop a model for predicting the risk of developing Alzheimer's disease as a function of age, exercise, and other variables.

Based on the data analyzed in this paper, it appears that the Gregory model overestimates the benefit of exercise and neglects the possible interference with sleep related to muscle ache and pain resulting from exercise. Equation 7 considers this effect on slow-wave sleep, which in turn affects the flushing equation (Equation 6). Equation 7 models three of the four datasets with high R^2 values and strong statistical significance based on the t-statistic. Equation 7 was not adequate to model the risk for dementia for the older women. An additional adjustment factor, Equation 8, was used to adjust the generation of the metabolic factors that are the source of the waste materials in the brain. This adjustment assumes that as VO_{2max} becomes low due to the combination of age and lack of exercise, the generation of these materials increases.

The mathematical model presented in this paper provides some indication that dementia, especially Alzheimer's disease, might be associated with the flushing process during slow-wave sleep as reported by Walker [7]. It also implies that as VO_{2max} becomes low, there is an enhanced benefit associated with aerobic exercise as measured in steps per day.

While the data from the meta-analysis by Ding *et al.* [1] is useful, it is limited because of the lack of association with age and gender. The model provided in this paper has not been tested for an all-male population. The model simulation for males implies that the benefit from exercise for older males is less than that for older women. Nevertheless, all the datasets considered, and the mathematical model provided in this paper indicate that there is high value in aerobic exercise as measured by steps/day for reducing the risk of developing dementia.

The model developed in this paper is based on several assumptions that have not been verified directly. The model should be used with caution. Nevertheless, it seems to simulate the measured data well. It may provide some direction for future research where both regular exercise and sleep are measured in middle-aged and older men and women in relation to the risk of developing dementia.

5. Conclusions

Both the measured data and the mathematical model that simulates the risk of developing dementia as a function of steps/day, gender, and age provide strong evidence that exercise can be used to reduce the risk of developing dementia. Mathematical model predictions closely match the measured data. The mathematical model has an advantage over the measured data by including gender and age as well as steps/day. Based on the age and gender effects as considered in the model, it is concluded that the data for the 84-year-old women as reported by Nguyen *et al.* [2] are valid measurements. While the model performs well in predicting risks compared to measured data, the assumptions on which the model is based have not been verified.

Conflicts of Interest

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

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