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Mathematical Model for Stroke and White Matter Hyperintensities

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Abstract

A mathematical model was developed to predict the risk of having a stroke as a person ages. The age component was derived from the concept that the change in risk of stroke with age is a function of the current risk of developing a stroke. This equation modeled the trend with age reported in the literature for two different data sets with R^2 values of 0.97 or better for both men and women. A second equation of a similar nature was developed to predict the accumulation of white matter hyperintensities, WMH, as a person ages. It appears that each equation includes a set of common risk factors. This set of common risk factors allows an individual's risk for stroke to be based on measured WMH. A third equation links WMH with the risk of developing a stroke. This equation allows an individual to use measured WMH from brain scans to predict the future risk of developing a stroke. In theory, a person with a relatively high measurement of WMH can project future risk for stroke with age and use counter measures such as exercise and medications to keep other risk factors low as a person continues to age.

Keywords

Stroke, White Matter Hyperintensities, WMH, Aging, Depression, Trauma, PTSD

1. Introduction

Stroke is a dreaded reality for ten to 15 percent of aging men and women. Stroke is personal for most people with a family member or close friend experiencing this debilitating event that often leads to death. Your author's father experienced multiple strokes and was forced into a nursing home for major care lasting almost ten years. He did not have a history of the common stroke risk factors. He did not smoke, drink, or have diabetes, heart disease, or high blood pressure. He was physically active until retirement age. He gained weight later in life and was

77 when the first stroke occurred. A close middle-aged friend, with migraine headaches, had an MRI as part of the migraine assessment. The neurologist noticed white matter hyperintensities, WMH, on the brain image and asked if this person had ever had a stroke. She had not had a stroke, but apparently, there is an association of WMH with strokes. Most people have never heard of WMH. What's the connection? Is the accumulation of WMH a risk factor or just an association? These questions seem worthy of a mathematical investigation.

White matter hyperintensities were discovered and first reported by Hachinski, *et al.* [1] in the 1980s. Now, nearly four decades later, WMH are considered part of the aging brain [2]-[7]. They are associated with stroke risk, risk for developing Alzheimer's disease, and other forms of cognitive decline, and health issues [3] [4] [8] [9] [10] [11]. Chen *et al.* [4] reported an odds ratio of 4.9 between WMH and lacunar infarcts, which strongly associated with risk of stroke. They are associated with small vessel disease [2]-[6] [8] [12] [13].

People who experience strokes often have elevated levels of WMH for their age [14]. Thurston, *et al.* [15] have linked WMH to exposure to trauma. Trauma early in life can alter the emotional response components of the Brain [16]:

> Childhood trauma is a potent risk factor for developing depression in adulthood, particularly in response to additional stress… childhood trauma in humans is associated with sensitization of the neuroendocrine stress response, glucocorticoid resistance, increased central corticotropin-releasing factor (CRB) activity, immune activation, and reduced hippocampal volume, closely paralleling several of the neuroendocrine features of depression.

It has been reported that 6.3 percent of children have been exposed to severe sexual abuse and 6.4 percent to severe physical abuse [17]. They also report that children exposed to severe sexual abuse had "abnormal thought and abnormal perception symptoms that were 2.25 and 4.08 times higher, respectively than the no exposure group." Unfortunately, what occurs early in life appears to have consequences later in life for depression, stroke, and accumulation of WMH.

Wolf, *et al.* [18] reported an early data set with risk of stroke as a function of age. They also reported relative risk or hazard ratios for most of the common risk factors for stroke: hypertension, diabetes, smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. Roy-O'Reilly and McCullough [19] provide an updated discussion of stroke pathology and differences associated with sex. Wolf, *et al.* [18] did not include depression, sedentary lifestyle, or exposure to trauma as risk factors. It is well documented, however, that having depression is associated with the risk of having a stroke [20]-[47]. Another risk factor, obesity, associates with depression and risk for stroke but also affects risk for high blood pressure, heart disease, and diabetes. Thus, obesity may not be an independent risk factor for stroke. Likewise, depression may not be independent from exposure to traumatic events, especially early in life. Trauma, however, seems to be an independent risk factor for both stroke and WMH [48] [15].

History of early life adversity such as the negative emotional trauma of a serious broken relationship and certainly sexual or physical abuse have been linked to risk of future stroke [25] [49] [50] [51]. The U. S. Department of Veterans Affairs [52] at their website reports that depression often occurs after trauma. They report 23 percent depression after the Oklahoma City bombing compared to 13 percent before the bombing. Perkins [53] reports that the American Psychiatric Association in 2013 re-categorized post-traumatic stress disorder, PTSD, as a trauma and stressor-related disorder. The new classification better fits the observation that patients often express shame and guilt associated with their experiences [53]. They also report that PTSD is an independent predictor of stroke and is also associated with the development of many risk factors for stroke.

Broken relationships after the development of romantic love are an emotional challenge and may lead to suicide, especially in men, and major depression in women [54]. Depression [49] may develop soon after the breakup and may also reappear later in life. These emotional and traumatic events, especially sexual trauma, appear to increase the risk for the buildup of white matter hyperintensities in parts of the brain [15], especially in women.

While Wolf *et al.* [18] developed a point system as an early mathematical model to predict stroke risk as a person ages, their procedure does not consider WMH, exercise, trauma, or depression. A simpler and more robust mathematical model is desirable.

Objectives

The objective of this work is to provide a mathematical model to predict cumulative ischemic stroke risk as a function of age, lifestyle choices, and certain medical risk factors, such as hypertension, diabetes, and cardiovascular disease. A second objective is to determine the relationship between WMH, a possible measure of emotional scarring, and risk of ischemic stroke.

2. Methods

2.1. Stroke Risk Equation

It is obvious from the literature [14] [15] [55] that the risk of ischemic stroke and WMH are related. Risk for both accumulates with aging and seems to be related to the same variables: hypertension, diabetes, smoking, and cardiovascular disease. Each system is complex and governed by maybe the same variables. It seems impossible now to determine if one causes the other. Certainly, both seem to be related to the development of cerebral small vessel disease [5] [11] [14] [56] [55]. Strokes occur without much warning other than risk factors. On the other hand, WMH can be detected by MRI technology relatively early in life and certainly by midlife. Coupling the two together mathematically might provide a valuable tool to detect and adjust lifestyle choices to slow down the risk of experiencing a stroke as a person ages.

As a starting point, it is assumed that the change in risk of developing a stroke

and maybe WMH over time can be expressed as the sum of small changes in the various risk factors—assaults on the brain through emotional trauma, physical trauma, and biological stressors. Some of these stressors may even be unknown at present time. This assumption is expressed in equation form as follows:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\partial R}{\partial A} + \frac{\partial R}{\partial BP} + \frac{\partial R}{\partial D} + \frac{\partial R}{\partial SM} + \frac{\partial R}{\partial CV} + \cdots \tag{1}$$

where, R = risk;

t = time;

A = age;

BP = blood pressure;

D = diabetes;

SM = smoking;

CV = cardiovascular disease.

One possible solution to an equation of this nature is to assume a product function. From this perspective, each of these partial differentials can be replaced by a hazard ratio or variable hazard ratio for each associated variable. The product represents an integrated solution to Equation (1).

Age is a measure of time and certainly an important variable in the development of stroke risk and WMH accumulation. Having had a stroke is a risk factor for another stroke: 15 times increased risk compared to the general population during the first year after the first stroke [57]. Mathematically the change in risk is related to the previous risk. This relationship can be expressed as

$$\frac{\mathrm{d}R}{\mathrm{d}t} = CR \tag{2}$$

where, C = calibration coefficient.

The first step to eliminate the differential is to separate variables:

$$\frac{\mathrm{d}R}{R} = C\mathrm{d}t \tag{3}$$

Next, Equation (3) can be integrated using boundary conditions for both sides:

$$\int_i^{R_A} \frac{\mathrm{d}R}{R} = C\int_0^A t \tag{4}$$

where, R_A = risk at specified age.

i = initial or reference risk.

Integration results in

$$\ln R_A - \ln i = CA \tag{5}$$

Equation (5) can be rewritten as

$$\ln \frac{R_A}{i} = CA \tag{6}$$

The natural log can be removed by taking the exponential of both sides:

$$R_A = ie^{CA} \tag{7}$$

From an odds or relative risk perspective, i will be set to 1.0. As a person ages, the risk of experiencing a stroke and maybe the accumulation of WMH volume should increase exponentially.

To complete the mathematical model, Equation (7) will be multiplied by the product of relative risk for all other risk factors:

$$R_A = R_0 O_{All} e^{CA} \tag{8}$$

where, R_0 = calibration variable; O_{All} = product of odds for all risk factors (O_{All} = 1.0 for reference population).

Next, stroke data from Wolf *et al.* [18] were analyzed. Their measured data are shown in Figure 1. Predicted curves using Equation (8) for men and women are shown. Equation (8) predicted the trend of the stroke data well with R^2 values of 0.99 for both men and women. In this and later analysis, a least squares minimization procedure between measured and predicted values in real space is used. The Student's t-test was used to evaluate significance (probability of model predicting a random effect). The significance level was also high ($p < 0.001$). Values for C are 0.08 for women and 0.054 for men. Values for R_0 are 0.0337 percent for women and 0.276 percent for men. Men have a much higher risk for stroke in young and mid-life years than women. Women in contrast start with a low risk but have a higher rate of increased risk with age.

2.2. WMH Accumulation Equation

Another key to this model development was measurements of WMH as a function of age reported by Habes *et al.* [58]. In their Figure 2, they show measurements of WMH volume in three groups as a function of age. The upper 20 percent of their measured WMH volumes were shown in red. The middle 60 percent were shown in grey, and the lower 20 percent were shown in black. While

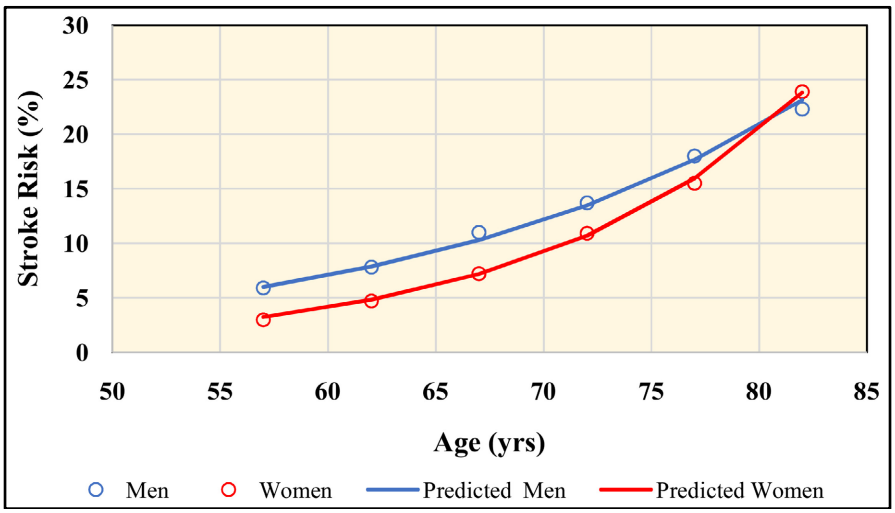

Figure 1. Measured stroke risk from Wolf, *et al.* [18] and predicted curves for men and women using Equation (8).

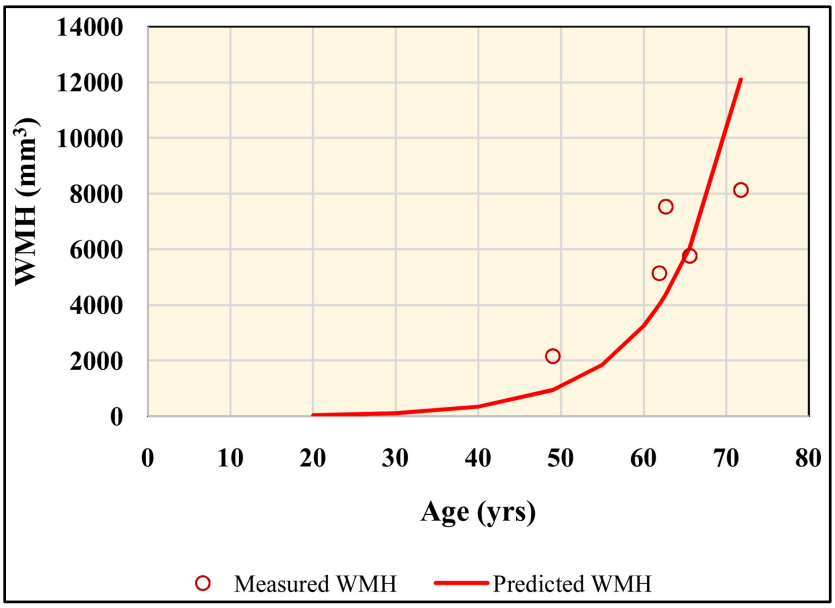

Figure 2. Comparison of measured WMH volumes and predictions with Equation (10). Data from [14].

there is much scatter, especially in their upper 20 percent, there is a clear relationship that appears to be an exponential increase with age at the interface between their red and grey data points. Points along this interface boundary were digitized from ages 40 through 80 years. The trend analysis in Excel was used to check the nature of the function. An exponential equation fits the data with an R^2 of 0.99:

$$V = 1.03\mathrm{e}^{0.1117A} \tag{9}$$

where, V = volume of WMH (mm^3); A = age (yrs).

It appears that the relationship associated with age in Equation (8) may also apply to WMH with C having a value of 0.1117. Obviously, R_0 must be replaced by a V_0 because WMH is measured in volume (mm^3 for the Habes *et al.*, [58] reference). The product of the dimensionless risk factors may or may not be the same. For now, it is hypothesized that they are closely related [55] resulting in the following:

$$V_A = V_0 O_{All} \mathrm{e}^{CA} \tag{10}$$

where, V_A = volume of WMH at specified age; V_0 = calibration variable (mm^3); O_{All} = product of all non-age risk factors (O_{All} = 1.0 for reference population).

Data from Habes *et al.* [58] was further analyzed to test the idea that $V_0 O_{All}$ might be the major variable in the development of WMH volumes. The results are shown in **Table 1**. All values in **Table 1** were computed with a C value of 0.1117. A value of 0.1 for $V_0 O_{All}$ produced a value of 142 for age 65—a rough estimate of the boundary between low 20 percent and middle 60 percent group. Individual points were impossible to read from their **Figure 2** for the lower 20 percent values.

Table 1. Predictions of WMH volumes (mm^3) from Equation (10) for variations in V_0O_{All}. Values for V_0O_{All} are shown in yellow at the top of this table. Calibration of V_0O_{All} values highlighted in yellow is based on data from Habes, *et al.* [58].

Age	0.1	0.5	1.03	4	8
	Very Low	Average	Medium Risk	High Risk	Very High Risk
0	0	1	**1**	**4**	**8**
10	0	2	**3**	**12**	**24**
20	1	5	**10**	**37**	**75**
30	3	14	**29**	**114**	**228**
40	9	44	**90**	**349**	**697**
50	27	133	**274**	**1066**	**2131**
55	47	233	**480**	**1863**	**3725**
59.1	74	368	**758**	**2945**	**5889**
65	142	711	**1466**	**5692**	**11,384**
70	249	1244	**2562**	**9950**	**19,899**
75	435	2174	**4479**	**17,393**	**34,785**
80	760	3800	**7829**	**30,403**	**60,806**

A value of 0.5 for V_0O_{All} produced a trend that approximated the middle location of the grey and black values in their Figure 2 from ages 40 to 80 years based on visual inspection. This location is an approximate estimate of average results excluding the extreme values in red. While the value of 0.5 is not precise, the resulting prediction of 368 for age 59.5 years is a close match to another data set for average conditions as discussed later. A value of 1.03 is a close match for the boundary between the grey and red points of their Figure 2 as discussed above. A value of 4 for V_0O_{All} produced a trend roughly midway based on visual inspection through the red points in their Figure 2, and a value of 8 for V_0O_{All} produced a trend near the upper limit of WMH volume from ages 40 to 80 years. Note that only single digit accuracy is implied for V_0O_{All} except for the 1.03 values. While there is much scatter in the data [58], there seems to be sufficient evidence to conclude that WMH increases with age according to Equation (10). The value in the square box for age 59.1 years will be discussed later.

2.3. Association between WMH and Stroke Risk

Is the relationship between stroke and WMH strong enough to combine risk factors for each? If true, then WHM volume can be used as an early detection methodology to access future stroke risk. Data from Giese *et al.* [14] was considered to answer this question. A summary of age and WMH from their data is shown in Table 2. All WMH are in or near the high or very high-risk columns in Table 1 in association with the reported age.

Table 2. Association of stroke subtypes with WMH. Data from [14].

Stroke Subtype	Age (years)	WMH (mm^3)
Cardioembolic Major Stroke	71.8	8130
Small Artery Occlusion	62.7	7530
Large Artery Atherosclerosis	65.6	5760
Undetermined	61.9	5140
Other	49.0	2160
All	**63.4**	**5860**

The ages given in this table were used with Equation (10) to compare predictions to the measured data. Results are shown in **Figure 2**. A value of 3.98 for V_0O_{All} was determined from the data to optimize the fit. An R^2 value of 0.86 was obtained which was significant ($p < 0.001$).

To relate back to stroke risk, Equation (10) was rearranged to solve for O_{All} using the age and measured WMH reported by Giese *et al.* [14]. A value of 0.5 from **Table 1** was used for an average/reference population calibration. Results are shown in **Table 3**. As might be expected, the O_{All} was extremely high for the strokes that occurred at a young age of 49 years.

The stroke risk for each of these groups using age and the computed O_{All} is provided for both male and female stroke patients as shown in **Table 3**. Giese *et al.* [14] also provided the percentage of females in each group. This information was used to compute a weighted average value for each age group. The average risk for stroke in this study based on WMH was almost 70 percent. All had strokes, but they are a subset of the general population. The prediction for men for age 62.7 (SAO, small artery occlusion stroke subtype) exceeded 100 percent. The average, standard deviation, and coefficient of variation were calculated excluding this age and stroke subtype. This elimination reduced the computed stroke risk to a little over 60 percent. It also reduced the relative scatter as measured by the coefficient of variation (standard deviation divided by mean) by approximately 50 percent. Adding seven years to all the ages resulted in a calculated average stroke risk of 96 percent excluding the SAO subtype. Subtracting seven years from all ages reduced the calculated average stroke risk to 40 percent. These calculated variations in age are well within the standard deviation reported by [14] for each age group. In this study, 100 percent of the people studied experienced a stroke. There is a high probability that others in the general population were close to having a stroke at the same age with similar amounts of WMH. Thus, predictions for the general population should be at a high risk but not 100 percent. It is highly probable that most of the strokes in the general population occurred or would occur within the 14-year window around the reported average age for each subtype.

Based on these calculations, it appears that the O_{All} generated from measured WMH may be the same as the O_{All} for stroke victims as hypothesized earlier. It

Table 3. Prediction of O_{All} and calculated stroke risk from measured WMH. Measured WHM, V_M, is from [14].

Age	O_{All}	R_A men	R_A women	Average	V_M	Female %	Stroke Subtype
49.0	18.1	68.8	32.0	52.3	2160	44.8	**Other**
61.9	10.2	77.7	50.6	67.0	5140	39.5	**Undetermined**
62.7	13.7	108.7	72.2	95.0	7530	37.7	**Small Artery Occlusion**
65.6	7.6	70.4	50.4	63.9	5760	32.3	**Large Artery Atherosclerosis**
71.8	5.3	69.4	58.4	64.3	8130	47.2	**Cardioembolic Major Stroke**
		Average		**68.5**	**61.9**[1]		
		Standard Deviation		**15.9**	**6.5**[1]		
		Coef. of Variation		**0.23**	**0.11**[1]		

[1]Average, standard deviation, and coefficient of variation not including small artery occlusion.

also is obvious that the risk of stroke is not associated with a fixed value of WMH. Instead, strokes occur when individual calculations using Equation (8) approach and exceed 40 percent. It appears that measured WMH can successfully be used to calibrate O_{All}. It also appears that a process to calculate O_{All} from a combined risk factors for stroke and WMH would be useful.

2.4. Evaluation of the O_{All} Variable

Wolf *et al.* [18] provided relative risk values for common risk factors for stroke. These values and the percentage of the population experiencing these risk factors are given in Table 4.

An individual's value for O_{All} is computed using the product of all risk factors that apply to the individual. The process was automated by programming a spreadsheet in Excel to make the calculation. The user enters a one for all risk factors that apply and a zero for all that do not apply for each risk factor. If no risk factors are checked, then the individual's O_{All} is 1.0. A value of 1.0 is less risk than the average O_{All} for the reference population. The O_{All} relative to the reference population is obtained by dividing the individual's O_{All} by the reference population O_{All}. The reference population's individual risk factors are computed with the following equation:

$$C_{RR} = 1 + \left(RF_{RR} - 1\right)\frac{RF_{\%}}{100} \tag{11}$$

where, C_{RR} = weighted population relative risk value for selected risk factor;

Table 4. Risk factors and relative risk for men and women. Data from Wolf, *et al.* [18].

Risk Factors	Men		Women	
	Relative Risk	Cohort %	Relative Risk	Cohort %
Systolic Blood Pressure	1.91	40.0[1]	1.68	40.0[1]
Diabetes	1.40	10.6	1.72	7.9
Smoking	1.67	33.8	1.70	26.4
Cardiovascular Disease	1.68	22.2	1.54	14.2
Atrial Fibrillation	1.83	2.8	3.16	2.2
Left ventricular hypertrophy	2.32	3.5	2.34	2.9

[1]Estimated value. Wolf, *et al.* state that hypertension is a major variable but do not give a percentage.

RF_{RR} = risk factor value (relative risk from Table 4);

$RF_{\%}$ = risk factor percentage in population.

The O_{All} computed for the population using the data in Table 4 is 2.15 for men and 1.87 for women. In Equation (8), the O_{All} value for the reference population is 1.0. A man with none of the risk factors in Table 4 would have (1/2.15) 47 percent of the risk of the average male member in the population. If he had all the listed risks, he would have an O_{All} value of 14.82 (31.85/2.15). A value of 14.82 is reasonably close to the 18.1 max value in Table 3. We will add other risk factors from other sources later in this development. A woman with no risk factors would have 54 percent of the risk of the average woman in the population. If a woman had all the risk factors, her O_{All} value would be 29.97. The average maximum value for 50 - 50 mix of men and women is 22.4—a value slightly larger than 18.1 in Table 3. These computed lower and upper values for O_{All} seem reasonable compared to values obtained in Table 3. Much of the elevated O_{All} for women compared to men is due to the relative risk of atrial fibrillation. If women had the same risk as men for this risk factor, the O_{All} drops to 17.6—a value very close to the 18.1 obtained from using measured WMH in Table 3 for calibration at 49 years of age. Based on the Atrial Fibrillation percentage in Table 4, only about two percent of people would experience this extreme risk for ischemic stroke.

Data presented by Wolf *et al.* [18] and used in this paper as a reference population for calibration is from the Framingham Study. Wolf *et al.* [18] do not give a percentage of the population at risk for elevated systolic blood pressure. A value of 40 percent was assumed for stage 2 high blood pressure (≥160/100 mm Hg) based on Vasan, *et al.* [59]. The work by Vasan *et al.* [59] was also based on the Framingham Study about a decade later than that reported by Wolf *et al.* [18]. There is some evidence of a dose response [61]. All things considered, the process of using the product of risk-factor functions seems to be on the right track in terms of mathematically modeling stroke risk.

Two other factors were added to the model to complete the calculation for individual risk: physical activity and traumatic life events. Willey *et al.* [61] report that moderate- to heavy-intensity physical activity results in a hazard ratio of 0.65 and that about 40 percent of the Northern Manhattan Study were physically inactive. This relationship was added to the model calculation procedure. It was assumed at this point that the physical activity in the Northern Manhattan Study and the Framingham Study were similar.

There is now growing and strong evidence that a major risk factor is missing from the factors presented by Wolf *et al.* [18]. In a broad sense, it is our exposure to stressful life events. Kornerup *et al.* [62] from a study in Denmark reported hazard ratio for stroke risk associated with life events. Their data is shown in Table 5. They reported that dealing with a critical illness in a close family member has a hazard ratio of 1.20—a 20 percent increase in risk for stroke. In contrast, dealing with children with a critical illness reduced the risk by 11 percent. These events seem related: both deal with critical illness but have opposite effects. One is personal one is not. It appears that some events in life can reduce stroke risk. It is uncertain as to why—maybe personality and job type. It is logical that financial, marital, and medical problems that are personal are major risk factors. They also report in their Table 3 that risk from life events accumulates increasing the risk of stroke. This observation agrees with Sareen (2014) that "There is a dose-response relation between severity and duration of traumatic event and the risk for development of PTSD." Dohrenwend *et al.* [63] also reported this relationship. Thus, there is evidence that the accumulation of traumatic events affects both mental problems and stroke. It is reasonable to expect that O_{All} increases with both the type and number of life events.

Next, information from Thurston *et al.* [15] was considered to include trauma as a variable in the prediction of O_{All} associated with WMH data. They focused on women with an average age of 59.1 years. Their study included two components: a survey of previous experiences of trauma events and measured WMH. They normalized their measurements by dividing by the intracranial volumes. They found that the single trauma most associated with WMH was sexual assault. In their Table 3, they provide a list of various trauma experiences. They

Table 5. Hazard Ratios are associated with some major life events. Data from Kornerup *et al.* [61].

Major Life Events	Percentage Increase	Hazard Ratio
Financial problems	60	1.60
Marital problems	28	1.28
Critical illness in close family	20	1.20
Children with education problems	0	1.00
Children with critical illness	−11	0.89
Conflict with adult children	−20	0.80

also compared WMH measurements for no sexual assault with WMH measurements for sexual assault. Normalized values for no sexual assault of 0.0032 and 0.0042 for sexual assault victims were determined from their Figure 1. Wikipedia in Brain Size [64] provides a value of 1130 cm^3 for intracranial volume for women. This value is close to the 1188 cm^3 value reported for women in India [65]. If we multiply the two normalized measured values by 1130, we get WMH in cm^3. Next, we multiply by 1000 to convert it to mm^3. The results are 362 mm^3 for no sexual assault and 475 mm^3 for sexual assault. The 362 mm^3 is very close to the 368 mm^3 in the square box in Table 1. The ratio of 475/362 results in hazard ratio of 1.31. In other words, sexual assault increased the risk of developing WMH by 31 percent.

Thurston, *et al.* [15] present data associated with risk from other traumatic events. Their data from their Table 3 for model 2 was used in Table 6 along with an adjusted calibration. They report a factor of 0.25 for sexual assault. The factors in Table 6 from Thurston's model 2 were multiplied by 0.31/0.25 to determine the percentage increase for the various single trauma types reported by Thurston, *et al.* [15].

Both data for stroke [62] and for WMH [15] are similar in magnitude. The average percent increase for each data set is 13. It appears from these two studies that traumatic events have a similar effect on stroke and WMH O_{All} values.

Based on the work of Heim *et al.* [16], people become more sensitive to trauma as trauma exposure increases, especially early in life. This theory can be expressed in differential form as

$$\frac{dR}{d\tau} = KR \tag{12}$$

where, R = risk as defined earlier;

τ = trauma exposure;

K = calibration coefficient.

Table 6. Hazard Ratios (HR) were determined for females from [15].

Trauma Event	Thurston Model 2	Percentage Increase
Sexual assault	0.25	31
Any trauma	0.24	30
Attacked, beaten, or mugged	0.20	25
Serious illness	0.12	15
Serious injury	0.10	12
Natural or human disaster	0.10	12
Serious accident	0.07	9
Workplace sexual harassment	0.03	4
Witness serious injury/death	0.02	2
Death of child	−0.10	−12

Following the same steps as used in the development from Equation (2) through Equation (7), the risk for exposure to trauma can be expressed as

$$HR_{\tau} = e^{KSE} \tag{13}$$

where, SE = sum of trauma exposure.

Equation (13) was used with results from [15] to determine the calibration value for K. The SE value in Equation (13) was set to 31 percent. The hazard ratio was set to 1.31 (1 + 31/100). Solving for K resulted in a value of 0.0087.

Next, data from [62] in **Table 4** for ischaemic stroke was used to test Equation (13). They used zero events as a reference and reported hazard ratios for 1 - 2 trauma events, 3-4 events, and over four events. Values for SE were estimated by multiplying the number of events by an average percentage increase determined by fitting predicted to measured data (**Table 7** and **Figure 3**).

A similar analysis was made for a linear model to predict the hazard increase associated with an increase in trauma events. A linear model also worked well with this data with a slightly lower R^2 value. The exponential model, however, was

Table 7. Comparison of measured and predicted values from Equation (13). Measured data from Kornerup, *et al.* [62]: **Table 4**, Ischæmic stroke for model C adjustments.

Number	*SE*	Measured	Predicted	Calibration
0	0	1.00	1.00	8.47% per event
1	8.47	1.07	1.08	
2	16.94	1.07	1.16	
3	25.41	1.25	1.25	
4	33.88	1.25	1.34	
5	42.35	1.57	1.45	
6	50.82	1.57	1.56	

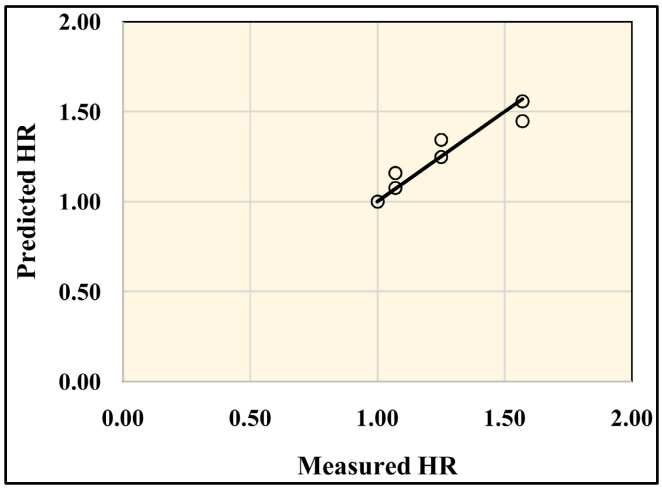

Figure 3. Comparison of measured and predicted hazard ratio for accumulating number of trauma events. Data from Kornerup *et al.* [62].

slightly closer to the measured values for all points.

This data set is complicated, especially the upper point. It is over four events; however, the exact value is unknown. While the R^2 of 0.99 is high, the significance is difficult to estimate. If we use all six points as shown in **Figure 3** and a loss of one degree of freedom because of the calibration, the significance is high ($p < 0.001$). If we use four points instead of the limits on each number of events, the result has about the same R^2 value and is still highly significant ($p < 0.001$). If we only use the lower three points, a high R^2 still results, but the significance drops ($p < 0.01$). The linear model is always good but never quite as good as the exponential model. Thus, based on the information from [16] and the data from [62], it is concluded that the exponential is the correct model to use for accumulating trauma events.

The major difference between the linear trauma and the exponential trauma model occurs at high accumulations of trauma. It is quite feasible that a woman with financial problems might live in a poor neighborhood, experience sexual assault, be mugged, and have marital problems. The sum of the percent increase for these four events (60 + 31+ 25 + 28) is 144 percent (hazard ratio of 2.44 for a linear model but 3.50 for the exponential model). Either number is high enough to place the woman in the red column in **Table 1** for WMH. If she develops high blood pressure and diabetes later in life, she has a value of 5.41 for O_{All} and a high probability (approximately 50 percent) of having a stroke by age 70 years. If she also develops heart disease, her value for O_{All} jumps to 8.33 and her risk for a stroke moves ahead by about five years to the mid-sixties. A man with the same trauma and risk factors has a 50 percent risk of stroke about five years ahead of the women. This example illustrates how a social-economic condition in life may lead to increased trauma and early stroke.

It appears that traumatic experiences truly bring an emotional toll on the brain and emotional scarring as evidenced with WMH. The evidence at this point seems to support the hypothesis that O_{All} is the same for both stroke and WMH accumulations.

2.5. Trauma, Depression, and Risk for Stroke and WMH

Building on the observation that traumatic events are additive in terms of risk for stroke, this subject will be explored further in this section. McCutcheon *et al.* [66] (2009) report that "Early exposure to assaultive trauma can influence risk for depression into adulthood". They also report that "women have a greater accumulation of assaultive events at earlier ages than men". Heim *et al.* [16] discuss how the exposure to trauma during childhood before age 13 leads to changes in brain function and risk for depression. There is little doubt that traumatic events have a cumulative effect on both depression and stroke risk. A question at this point is whether to add depression as an independent risk factor for stroke and WMH.

Brown [49] states that depression is both biological and dependent on social

interactions. It has its origins in the quality of core social roles. He provides qualitative evidence that certain life stress items are additive in risk for developing depression. He defines the nature of these stress items as loss of a lover, spouse, parent, or job, etc.; humiliation or embarrassment by lover, spouse, boss, parent, etc.; chronic humiliation or putdown by parent, teacher, or boss often leading to feelings of entrapment. These stressful events attack a person's self-esteem, value, confidence in life and often develop with little opportunity to escape. Brown's discussion helps explain why traumatic events are additive as reported in the literature [48] [62] [63] [66].

It is reported that depression is 3 to 5 times more likely in those with PTSD than those without PTSD [52]. Logically, traumatic life events accumulate and lead to early-onset depression, and increased risk for stroke later in life.

PTSD is higher among veterans but not limited to military service. Schnurr [67] reports on the VA Health Care website that lifetime prevalence of PTSD is 8 percent in women and 4 percent in men. The prevalence is about 50 percent higher in veterans: 13 percent for women and 6 percent for men. Obviously, people with PTSD are at an elevated risk of developing depression and stroke.

Because the accumulation of traumatic life events is linked to both increased risk for stroke and the accumulation of WMH, does the development of depression associated with trauma further increase the risk for stroke? Dong *et al.* [68] reported a pooled relative risk of 1.34 after adjusting for confounding factors. This value is roughly the same as the average relative risk values in **Table 5** for the trauma events that are greater than 1.0. It is possible that trauma expresses its effects first with depression and later in life with strokes and WMH, but that having depression does not increase the risk for stroke or WMH beyond that of the trauma. Similar results were reported by Barlinn, *et al.* [69]: relative risk of 1.40. There was considerable overlap of data between the two studies. Also, both studies reported a high risk of stroke that exceed three standard deviations from mean values. These extreme stroke relative risk values are analyzed next.

Both Dong, *et al.* [68] and Barlinn *et al.* [69] report a value of 3.41 for relative risk of stroke related to depression from Kamphuis, *et al.* [28]. The Kamphuis publication was reviewed to determine why it was an outlier. Their reported relative risk for stroke was 1.35 in contrast to the 3.41 value reported by Dong *et al.* [68] and Barlinn, *et al.* [69]. Obviously, an error was made and copied.

Next, a value of 2.6 reported by Dong *et al.* [68] from Liebetrau *et al.* [44] (2008) was investigated. Again, the reported relative risk values do not match that in the original paper. Liebetrau, *et al.* [44] reported a relative risk of 3.8 for demented and 2.4 for non-demented patients 85 years of age. These numbers are high and seem to be associated with late-onset depression instead of early-onset depression. These extreme values were not considered further.

Another outlier reported by both Dong, *et al.* [68] and Barlinn *et al.* [69] was referenced in a publication by Larson, *et al.* [42]. The study reported relative risk by age groups. They also reported that "The group of respondents with depressive disorder was slightly more likely than those with no disorder to report an

incident stroke (RR = 1.2)". The higher stroke risk that was reported seemed to be complicated by low education, age, and low economic status.

The most interesting outlier of 4.63 was from Gafarov *et al.* [70]. The result was for women aged 25 - 64. The young age eliminates late-onset depression. Depressed women in this study were observed to have a 2.53 relative risk of developing myocardial infraction. If the relative risk of 1.54 for women with cardiovascular disease reported by Wolf *et al.* [18] in **Table 4** is used with the 2.53 value for developing myocardial infarction, a relative risk of developing a stroke is 3.90. This leaves a value of 1.19 for relative risk related to depression and stroke. The women in the study by Gafarov *et al.* [70] were randomly selected for the study. Stress at work and social-economic conditions should be the same for the depressed and nondepressed groups. It is possible that prior trauma events occurred and led to the depression. Depression causes stress in relationships. Thus, the depressed group should have had more marital problems as reported in the study.

It appears at this point that traumatic events in life are an important input for the development of depression. The risk of developing a stroke, however, probably does not increase with the expression of depression. Depression certainly is not independent of trauma.

We should not forget that there is a biological component to depression. Not all people exposed to trauma will develop depression.

Based on the qualitative assessment of events leading to depression reported by Brown [49] an attempt was made to expand and roughly quantify the risk for stroke and WMH based on the nature of his grouping of stress items. These events and rough calibration are presented in **Table 8** and are intended to supplement the measured values in **Table 5** and **Table 6**. The reader is cautioned that the calibration is based on judgment and not direct measurement.

Note that the calibration for many of the components in **Table 8** is based on data from [15] and maybe most appropriate for females. The humiliation/used item for rejection by lover and loss of virginity is certainly restricted to females and is based in part on data in **Figure 4**. There is a spike in divorce rate associated with two premarital sex partners. One way to explain this spike is that some females will feel sexual shame and depression associated with loss of virginity before marriage—a possible explanation for the 10 percent increase in risk for divorce over no premarital sex in **Figure 4**. If she marries her lover, she would be on the bottom curve (**Figure 4**). If she is invested in her lover expecting to marry him but is dumped instead, she has experienced two traumatic events: loss of virginity and loss of romantic lover. She has two major stress items as she moves on in life to the next relationship. The estimated value of 60 is the sum of 30 for sexual trauma (loss of virginity) and 30 for loss of expected husband. This analysis is in line with sexual abuse, emotional abuse, bullying, and rejection discussed by Wagner [71] (2016). Note that the divorce rate after five years of marriage [72] increases by 10 in association with one sexual partner before marriage (loss of virginity) and another 10 (probably associated with rejection by

Table 8. Estimated life stress factors.

General Stress Types	Increase %
Chronic Emotional Stress	
Humiliation/putdown (verbal abuse from parent)	30
Child sexual abuse	30
Consensual teenage sexual manipulation (sexual trauma)	30
Consensual adult sexual manipulation (sexual trauma)	15
Sexual sin (physical adultery, emotional adultery, pornography)	15
Humiliation/embarrassment (brother, sister, parent)	15
Acute Emotional Stress	
Humiliation/Used (rejection by romantic and first sexual partner)[1]	60
Humiliation (infidelity by lover)	30
Example Application for Female	
Humiliation: Embarrassing brother	15
Humiliation: Embarrassing father	15
Consensual teenage sexual manipulation (sexual trauma)	30
Humiliation (infidelity by lover)	30
Rejection by first lover who took virginity	60
Martial problems	28
Serious illness	15
Sum	**193**

[1]For females only.

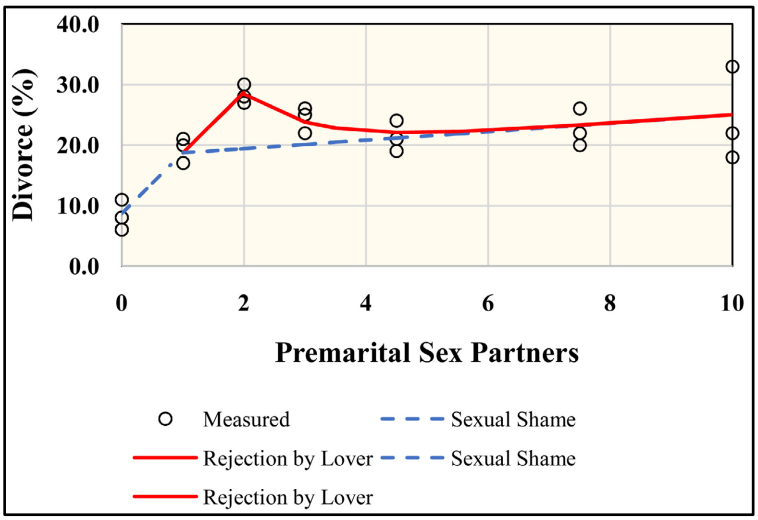

Figure 4. Association of premarital sex partners and divorce rate illustrating the possible trauma effects of loss of virginity and rejection by lover before marriage. Data from Wolfinger [72].

first lover) before the second premarital sex partner (probably her husband) before marriage.

Based on Brown [49] and data from McCutcheon *et al.* [65] and Heim *et al.* [16], depression often has stress triggers, such as trauma. Depression defined as being mentally distressed is a major factor in divorce [73]. Both the number and intensity of emotional abuse are associated with decline in mental health scores [74]. While depression may not directly relate to increased risk for stroke and accumulation of WMH, the stress triggers seem to increase the risk for both stroke and WMH.

A trauma component was added to the stroke and WMH models. For the trauma component, a user enters the sum of trauma values obtained from **Table 5**, **Table 6**, and **Table 8**. This sum in percent is converted to relative risk using Equation (13). To relate back to the calibration data set, it was assumed that the two added components of exercise and trauma were embedded in the data set presented by Wolf, *et al.* [18] and that the two components offset each other in terms of population risk.

Merrick *et al.* [51] report that approximately three-fifths of their 25-state study population experienced at least one traumatic event. They also reported that one-sixth of the population had four or more events. A value of 60 percent with a relative risk of 1.446 was used in the Excel model. This combination offset the reduction in risk from physical activity and produced the same population risk as the original data from Wolf *et al.* [18].

As a mathematical check, four stress items of 25 percent were used in Equation (13) times 1/6 plus one 25 percent stress item in Equation (13) times 5/6 was used. The resulting weighted average value for relative risk is 1.434. This value is reasonably close to the value of 1.446 used in the Excel Model.

3. Results

Wolf, *et al.* [18] developed a mathematical process to estimate the risk of having a stroke using a point system. Their process seems detailed and complicated. It does not consider the accumulation of WMH as a possible input to calibrate and give an early projection of stroke risk.

A mathematical model alternative is developed in this paper based on the logic of the sum of partial differential changes for the various risk factors. A product solution was assumed and tested based on the relative risk of each risk factor presented by Wolf, *et al.* [18]. Two additional risk factors were added to the original work of Wolf, *et al.* [18]: physical activity and trauma from life events. Equation (8) was derived to predict stroke risk and was calibrated for men and women from the data reported by [18]. Predictions with Equation (8) matched measured values from [18] with an R^2 of 0.99 for both men and women and were highly significant ($p < 0.001$).

A second and similar equation was developed to predict the accumulation of WMH with age. This model, Equation (10), was used with data from Giese *et al.*

[14] to predict the accumulation of WMH for people who had experienced strokes at various ages. Predictions with Equation (10) matched measured values with an R^2 of 0.86, which was significant ($p < 0.001$).

By assuming the variable for product of risk factors, O_{All} is the same in Equations (8) and (10), it is possible to use measured values of WMH to calibrate Equation (8) for an individual's value of WMH to project future risk of developing a stroke. Equation (14) shows this relationship:

$$R_A = R_0 \left(\frac{V_M}{0.5e^{0.1117 A_M}} \right) e^{CA} \tag{14}$$

where, V_M = measured WMH; A_M = age at which WMH was measured.

Equation (14) can be used to project the future risk of developing a stroke as a function of age after calibration with measured WMH. If another risk factor develops after the WMH measurement, the V_M value should be multiplied by the new relative risk for the new risk factor. If other risk factors existed before the measurement of WMH, they should already be included through the WMH measurement and should not be considered as new risk factors.

Next, Equation (8) was evaluated with a stroke data set from Kelly-Hayes [75]. These data are for a later period and should reflect some treatment benefits for managing blood pressure and medications to reduce the risk of stroke from heart disease etc. Equation (8) was recalibrated to fit this data set. After recalibration, predictions matched the measured data with an R^2 of 0.97 for both men and women. Values for C were held constant at 0.054 for men and 0.080 for women. Values for O_{All} were reduced to 0.499 for men and 0.515 for women. Both the measured and predicted values for men and women for the data from Wolf *et al.* [18] and Kelly-Hayes [75] are shown in **Figure 5**.

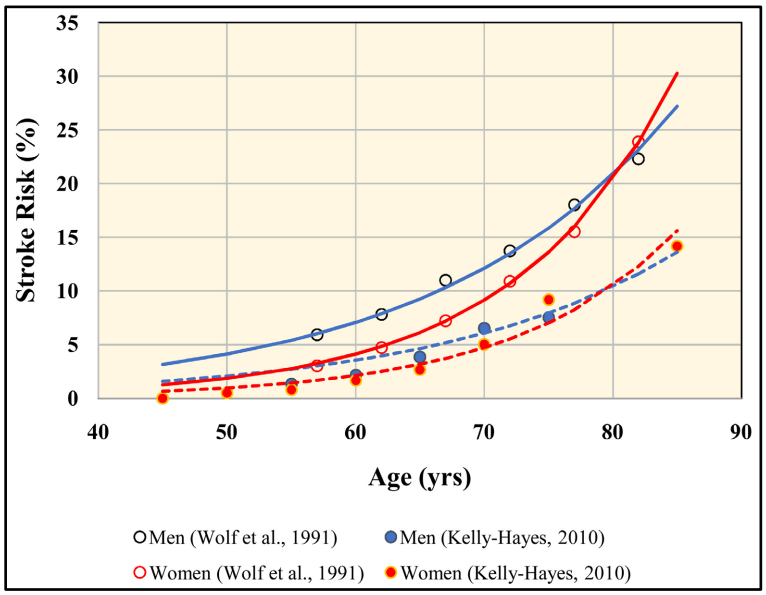

Figure 5. Comparison of measured data sets and predictions for each data set. Data from Wolf *et al.* [18] and Kelly-Hayes [75].

4. Discussion

It is concluded at this point that Equations (8) and (10) are adequate mathematical models to predict stroke and WMH changes with age. By assuming that the O_{All} variable is the same in both equations, Equations (8) and (10) can be combined into one equation that allows an individual calibration for stroke risk based on measured WMH. Equation (14) provides this combined model. Data from Giese, *et al.* [14] appear to follow this relationship. Based on the report [50] that 10 to 14 percent of ischemic strokes occur in adults between the ages of 18 and 45, it appears that a strong need exists, such as the use of WMH calibration, for early assessment of stroke risks. It also appears that early assessment of exposure to trauma is essential to know the potential for early onset of a stroke. Treatment for PTSD should be pursued for these individuals as early as possible.

There are two perspectives of interest for stroke and WMH analysis: individual assessment and population risk analysis. The risk variable, O_{All} in the current model is the product of several relative risk factors: systolic blood pressure, diabetes, smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy from [18] plus trauma and physical activity. These values vary with gender.

An Excel model was programmed to compute the O_{All} value for an individual and for a population compared to the data from Wolf *et al.* [18]. This O_{All} calculator is shown in **Figure 6**. Input data is through cells with a green background. If the reduction fraction for each risk factor is set to zero, the O_{All} for the cohort population becomes 1.0 as illustrated in this table for men.

Input data for an individual is with the bottom row with green background. If an individual has a risk factor, that risk factor is entered with a 1 in the appropriate green cell. Two exceptions are physical activity and trauma. An entry of 1 for physical activity produces a reduction in risk. The user enters a sum of trauma risk as discussed earlier in this paper. The R_0 is 0.276 and 0.0337 respectively for men and women as shown in the third column and bottom cell in each of the tables. The value above this calibration is the calibration for WMH.

Both the individual risk and population risk differ for men and women when the individual input is the same. Note that the minimum predicted individual risk for men is 0.30 compared to 0.35 for women for the exact same input when blood type is unknown. Cohort risk is different for men compared to women even when there is no reduction fraction due to modern treatments for the various risk factor. This difference occurs because the population percentages and the relative risk values vary between men and women.

As discussed earlier, the stroke data for men and women reported by Kelly-Hayes [75] is about 50 percent lower than that reported by Wolf *et al.* [18]. The example in **Figure 6** for women illustrates one way for this reduction to occur for a cohort using modern technology. Obviously, there are unlimited possible combinations for this reduction to occur.

Values in orange are the relative risk values reported in the literature primarily

Men								
Data	1.446	40	40	1.4	33.8	1.68	1.83	3.5
Reduction	0	0	0	0	0	0	0	0
Percent	60	40	40	10.6	33.8	22.2	2.8	3.5
Relative Risk	1.446	0.65	1.91	1.4	1.67	1.68	1.83	2.32
Blood Type	0.446	-0.35	0.91	0.4	0.67	0.68	0.83	1.32
Unknown 1.00	**Trauma**	**Physically Active**	**Systolic BP Men**	**Diabetes Men**	**Smoking Men**	**CV Disease Men**	**Atrial Fibrillation**	**Left VH**
	0	1	0	0	0	0	0	0
0.65	1.00	0.65	1	1	1	1	1	1
Cohort Adj	1.268	0.790	1.364	1.042	1.226	1.151	1.023	1.046
Cohort Risk	**2.152**	**Individual Risk**		**0.65**	**Individual O_{all} =**		0.30	
WMH V_0O_{all} =	0.151	0.50	Habes 2016		**Cohort O_{all} =**		**1.00**	
Stroke R_0O_{all} =	0.083	0.276	Wolf 1991					
Women								
Data	1.446	40	40	1.72	26.4	1.54	3.16	2.9
Reduction	0.5	0	0.9	0.9	0.8	0.9	0.9	0
Percent	60	40	4	7.9	5.28	14.2	2.20	2.9
Relative Risk	1.223	0.65	1.68	1.072	1.7	1.054	1.216	2.34
Blood Type	0.223	-0.35	0.68	0.072	0.7	0.054	0.216	1.34
O 0.88	**Trauma**	**Physically Active**	**Systolic BP Women**	**Diabetes Women**	**Smoking Women**	**CV Disease Women**	**Atrial Fibrillation**	**Left VH**
	0	1	0	0	0	0	0	0
0.65	1.00	0.65	1	1	1	1	1	1
Cohort Adj	1.067	0.790	1.027	1.001	1.037	1.001	1.000	1.039
Cohort Risk	0.934	**Individual Risk**		**0.65**	**Individual O_{all} =**		0.31	
WMH V_0O_{all} =	0.153	0.50	Habes 2016		**Cohort O_{all} =**		**0.50**	
Stroke R_0O_{all} =	0.0103	0.0337	Wolf 1991					

Figure 6. Excel tables to calculate individual and cohort O_{All} values for men and women.

from Wolf, *et al.* [18]. Population risk can change because the percentage of people with risk is reduced, such as reduced smoking, or improved medical treatments are used, such as the use of statins and other medications, to reduce the relative risk. The percentage of the population with risk is shown in yellow background. The top row in each table is the reference data. The reduction input data reduces the top value to the value with the same color background in the cell below.

The bottom cell in the second column for both tables is the value used in Equ-

ation (8) to make a prediction as a function of age. The value above is the number used in Equation (10) to estimate WMH.

It is assumed that the individual user will adopt modern technology. Thus, when the orange background values are reduced, both the individual and cohort risk are computed with the reduced value.

This model does not do transitions. For example, if an individual quits smoking, he or she is given the full benefit of not smoking. Nevertheless, the model should help an individual to understand the impact of lifestyle choices, such as physical activity, smoking, medications for heart disease, medications for blood pressure, etc.

Gaffey and Sico [25] provide a table of traditional risk factors including all that is included in **Figure 5**. They also mention obesity, lipid disorders, and obstructive sleep apnea. They list nontraditional risk factors including trauma/PTSD, migraine, illicit drug use, pregnancy, oral contraceptives, insomnia, and depression. These factors are not considered in this paper. They may account for the 0.30 to 0.31 O_{all} values unexplained in the current model. On the other hand, many of these factors may not be independent of other factors. For example, poor sleep and depression probably are not independent of trauma. More research is recommended to tease out the remaining risk factors.

The development in this paper started with a partial differential equation summing the changes in risks from the various independent variables. It was assumed that the solution to this equation could be expressed as a product function of the independent variables. At this point, there is sufficient evidence to conclude that this assumption is valid.

In the early 1970s, the hand-held calculator became available. Before these devices were created, engineers and science majors performed multiplication and division operations with a slide ruler. The ruler illustrates the process used in this paper. Each of the integrated partial differential functions in Equation (1) represents the natural log of the respective relative risk function. The derivation of Equation (8) illustrates this relationship for effects of age. The change between Equation (6) and Equation (7) illustrates the change from natural log space and normal space. Equation (13) also illustrates a relationship between the natural log and non-log mathematical space for trauma. It may be possible to derive relationships for other risk factors using a similar methodology. As an example, data from Kannel *et al.* [60] for risk of developing Atherothrombotic brain infarction follows an exponential equation of similar form as Equation (8) using systolic blood pressure as the independent variable. This function was not used in this paper because of the unknown percentage of the population with a given level of systolic blood pressure. Nevertheless, it illustrates a dosage relationship to blood pressure.

All risk factors may not be a dose-response relationship. Risk factors, such as diabetes and heart disease, are controlled in part by genetics: either you do or do not have the risk. If you don't have the risk, the relative risk is 1.0 and the natural log of 1.0 is zero. If you have these risks, there now exists treatments to re-

duce the risk. For example, cholesterol medication and reduced saturated fat diets affect the risk of developing heart disease. This information was mathematically associated with reduced risk of developing Alzheimer's disease [76] and probably has a similar effect in reducing risk of stroke. The level of aerobic exercise as measured by VO_{2max} also was shown to affect the risk of heart failure [77]. These treatments can be considered through the reduction input in green boxes for each risk factor in **Figure 6**.

Note that in **Figure 6**, Blood type is considered. Jaworek *et al.* [78] reported that people with Type A blood have a 16 percent increase in risk for ischemic stroke. People with type B have a 5 percent increase in risk, and people with type O have a reduced risk of 12 percent. Having Type AB blood is a relatively low probability but has an 83 percent increase in stroke risk compared to Type O [79]. They also reported an interaction with risk for diabetes.

5. Conclusions

While there is much more research needed, it is commendable that the data presented by Kelly-Hayes [75] indicates approximately a 50 percent reduction in stroke risk during the last two decades. Early assessment seems to be a key to management of stroke risk. People with known severe traumatic experiences should consider themselves warned for possible stroke early in life. For people with numerous traumatic experiences, especially early in life, a measurement of WMH may be useful to apply Equation (14) to project future risk of stroke. Lifestyle choices at this point should strongly be evaluated. Smoking should be stopped. Aerobic physical activity should be pursued. If depression has occurred, consider this development as an early indication that your body and mind may have reacted to trauma. Get professional help.

The relationship between age and stroke has been studied intensively. The derivation of Equations (8) and (10) helps to explain the nature of age effects on stroke risk and WMH accumulation. Equation (14) that links stroke risk and measured WMH has the potential to help high risk individuals to better monitor their stroke risk as they age. Finally, understanding that existing risk factors can be expressed and analyzed in natural log space may also have value in future research.

Conflicts of Interest

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

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