Advanced Healthcare Services Leading to Relax Natural Selection May Have Been Contributing to Global and Regional Increase of Dementia Incidence

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Research Article

Abstract

Background

Ageing and genetic traits can only explain the increasing dementia incidence partially. Advanced healthcare services allowing dementia patients to survive natural selection (die of dementia) and pass their genes onto their next generation.

Methods

Country-specific estimates of dementia incidence rates (all ages and 15-49 years old), Biology State Index (I_s) expressing reduced natural selection, ageing indexed by life expectancy $e_{(65)}$, GDP PPP and urbanization were obtained for analysing the global and regional correlations between reduced natural selection and dementia incidence rate with SPSS v. 27.

Results

Worldwide, both I_s significantly, but inversely, correlated to dementia incidence rates for both populations in bivariate correlations. These relationships remained in the populations of all ages and 15-49 years old regardless of the competing contributing effects from ageing, GDP and urbanization in partial correlation model. Enter multiple linear regression showed that I_s was the significant predictor of dementia incidence in populations of all ages and 15-49 years old. Subsequently, I_s was selected as the variable having the greatest influence on dementia incidence in stepwise multiple linear regression. I_s corelated to dementia incidence more strongly in developed population groupings.

Conclusions

Worldwide, reduced natural selection may be another the significant contributor to the increasing dementia incidence with special regard to developed population.

Background

Dementia is not one specific disease, but a syndrome that affects patient's ability to perform everyday activities due to a chronic or progressive deterioration of memory, thinking and behaviour [1]. Worldwide, around 50 million people are being affected by Alzheimer's (60-70%), vascular diseases (20-30%), Lewy bodies and frontotemporal dementia [1, 2]. Worldwide, dementia not only affects individual patients whose human right and freedom are unnecessarily restricted and subject to social stigma, but also has had tremendous impact on families, caregivers, and society [1, 3].

Although extensive studies have been conducted to explore the etiological factors, but only ageing and genetic susceptibility are constantly postulated as the risk factors [4]. Nevertheless, increasing evidence have shown that, as the commodities of dementia, chronic health conditions (e.g. diabetes, obesity hypertension and cerebrovascular lesions) and their associated lifestyles (e.g. cigarette smoking, lack of

exercise and social engagement, gluten and meat eating) have been postulated as the potential risk factors of dementia [5].

The World Health Organization (WHO) estimated that, worldwide, the annual incidence of dementia is nearly 10 million and which will make the number of people diagnosed dementia exponentially rise up to 82 million in 2030 and 152 in 2050 [1]. The similar trends were also reported in a number of individual countries, such as United Kingdoms, China, Australia and United States. Population ageing has been the only attributable risk factor to explain this exponential increase of annual incidence at population level [1]. Almost all the studies only included that the increase of population aged 65+ is the contributing to the increasing presence of dementia.

Henneberg and Piontek advanced the Biological State Index (I_{bs}) based on the calculation of population specific fertility and mortality data [6, 7]. The I_{bs} signifies the specific portion of population who can survive their reproduction period (50+ years old). A number of publications co-authored by Henneberg revealed that the percentages of populations in different population surviving their reproduction cycle varying between 63.5% (Burkina Faso) and 99.4% (Iceland and Cyprus), and the average was 92.8% [8–11].

It is a common sense that advanced healthcare services have allowed more and more people to survive their reproduction periods successfully. From the perspective of Darwinism, the underlying reason is that advanced healthcare services have relaxed natural selection leading to low mortality [12]. Naturally, with the increasing portion of population participating in the successful reproduction, a concern has been raised that the chance for deleterious genes/mutations of chronical diseases pass onto their next generations has been and will be increased [13]. The consequence of this accumulating process is that human population is subject to increasing incidence of non-communicable diseases. Dementia is an umbrella term caused by a number of non-communicable diseases with genetic traits, which can be passed onto their next generation.

The genetic traits of dementia have two sources: 1) directly from those causing dementia including Alzheimer's, vascular, Lewy bodies and frontotemporal diseases; 2) from the comorbidities (chronical diseases: diabetes [10, 14], obesity [8, 9], hypertension, mental health disorders). Modern healthcare services have made it possible that population carrying genes/mutations of dementia diseases or its comorbidities are free of dementia presence for all their life, or presented with dementia, but still healthy enough. This population can marry and reproduce and pass their dementia related genes/mutation to their generation. The portion of population surviving the reproduction period (dying after 50+) determines the level of the deleterious genes to be inherited by their next generation. Inspired by this concept and previous studies testing the accumulating possibilities of deleterious genes in human populations due to relaxed natural selection, we obtained population specific empirical and macro-level data to examine, from a worldwide perspective, that population with high level of relaxed natural selection has higher dementia incidence.

Materials And Methods

Data sources

The dependent variable are the population specific incidence rate of "Alzheimer's disease and other dementias (dementia hereafter) " published by the Institute for Health Metrics and Evaluation in 2020 [15, 16].

The estimate of dementia incidence rate is expressed as the number of people per 100,000 were diagnosed with dementia in 2019 which were caused by Alzheimer's disease and other related diseases.

In this cross-sectional study, natural selection is the essential part of the study method, and it is primarily related to reproduction. Therefore, the dementia incident rates for populations of both all ages and 15-49 years old were extracted for data analysis respectively to explain the accumulation of dementia genes/mutation at population level.

The predicting variable is current population specific level of natural selection (Darwin fitness) extracted from the previous publications [8, 9, 11].

The level of reduced natural selection is measured with the Biological State Index (I_{bs}) which was calculated with the population specific fertility and mortality data published by United Nations (2008) and WHO (2012) respectively [17, 18]. The Biological State Index (I_{bs}) presents the probability that an average individual born into a population is able to fully participate in the reproduction of the next generation in order to pass their genes/mutation to their offspring [6–8]. Considering that the prime criterion of Darwinian fitness (adaptive success) is successful reproduction [19, 20], Darwin fitness (I_s) was calculated with the formula, $I_s = (1-I_{bs})/I_{bs}$, which was considered as the independent variable [8, 11, 20].

Except for ageing, the two variables (GDP and urbanization) which have been associated with dementia were also included as the potential competing variable for data analysis:

1) Ageing expressed with Life expectancy at 65 years old (Life $e_{(65)}$, 2010-2015) published the United Nations. This study did not take life expectancy at birth because dementia is more common in people over the age of 65, although it can also affect younger people. Another consideration for us to include Life $e_{(65)}$ is that the biopsychosocial functioning of people starts to decline from that age.

2) GDP PPP is expressed in per capita purchasing power parity in 2015 US dollars published by the World Bank [21]. GDP PPP has been associated with prevalence rate of dementia, and it also determines the level of healthcare services with special consideration of the screening rate for successful and accurate dementia diagnosing for this study.

3) Urbanization is expressed in the percent of population living in urban areas in 2015 published by the World Bank [21]. Urbanization entails a high level of education, but a poor lifestyle, for example, lack of lack of exercise and social engagement, consumption of food with few nutritional benefits, more gluten

and meat eating, air pollution, and consuming more salt, fat, sugar and alcohol. Urban lifestyle has been postulated as a complex risk factor for chronic diseases [22].

We extracted a list of 204 populations with dementia incidence rates in 2019, and then we downloaded population specific I_s (also measuring Darwin Fitness), Life $e_{(65)}$, GDP PPP and urbanization before matching them with the dementia incidence list. A set of the population specific data for 204 countries were obtained and stored in the Microsoft Excel® for data analyses. For some populations, the estimate of one or the other variable was missing, thus specific analyses have sample sizes varying from 182 to 204. Each population was treated as an individual study subject and all of their available information was analysed.

In order to demonstrate the universal predicting effect of reduced natural selection (Darwin Fitness) on dementia incidence rate, the populations were grouped for further correlation analyses based on: 1) the WHO geographic regions [23]; 2) the World Bank income classifications [24]; 3) the United Nations gross national income (GNI) classifications [25]; 4) the strong contrast in terms of geographic distributions, per capita GDP PPP levels and cultural backgrounds to get seven population groupings: Asia Cooperation Dialogue (ACD) [26], the Asia-Pacific Economic Cooperation (APEC) [27], the Arab World [27], Population with English as the official language (extracted from personal knowledge and experience), Latin America and the Caribbean (LAC) [28], Organization for Economic Co-operation and Development (OECD) [27], and Southern African Development Community (SADC) [29]. In these analyses, we only included those populations for which we could access their data for the specific groupings. Except for population with English as the official language, all the other population listings are sourced from their respective official websites before matching them with the list of populations with dementia incidence rate. Grouping population in consideration of geographic locations, cultural background and ethnicities for analysis also allowed us to align our findings against those reported in the previous local or regional studies regarding heterogeneous dementia epidemiology.

Data analysis

To examine the relationships between Darwin fitness and dementia incidence rate in different data analysis models, the analysis proceeded in four (4) steps:

1) Populations were integrated into the geographic map depending their locations. The darkness of colour for their areas in the map varies with their level of I_s (Darwin fitness). For mapping clarity and more populations to be included in the map, the population label on the map is indicated as the ISO code of the population instead of the full name.

Scatter plots were also conducted for exploring and visualizing the correlation between the Darwin fitness and dementia incidence rates at population level. Data quality and variable distributions can be examined in scatter plots as well. Mapping Darwin fitness, calculations of mean I_s, sample size and standard

deviation, and producing scatter plots were conducted in Excel (Microsoft® 2016) with raw data (not log-transformed).

The 204 countries were also grouped as per the WHO geographic classifications for comparing mean I_s in different regions.

Before running correlation analyses all data were logarithmed, which reduced possible curvilinearity of regressions and data non-homoscedasticity due to their heretical distributions.

2. Bivariate correlations (Pearson's and nonparametric) were conducted to examine the strength and direction of the correlations between all variables.

Bivariate correlations were also performed for each data set of grouped populations to further explore and compare the correlations between I_s and dementia incidence rate.

3. Partial correlation of Pearson's moment-product correlation was performed to examine the correlation between Darwin fitness and dementia incidence rate while the competing variables (ageing, GDP PPP and urbanization) were kept statistically constant.

We alternated the four variables (I_s, ageing, GDP PPP and urbanization) as the predicting variable to explore its relationship with dementia incidence rate while controlling for all the other three variables. Thus, we can analyse and compare the levels of the independent correlations between dementia incidence and each of four potential risk factors [30, 31].

4. Standard multiple linear regression (enter model) was conducted to analyze the correlations between dementia incidence rate and each of the four predicting variables. Subsequently, stepwise linear regression was performed to select the predictor(s) having the best influencing effects on dementia incidence.

In the above Steps 2-4, dementia incidence rates were alternated as the dependent variables for data analyses, and results were reported in parallel.

Bivariate correlations, Pearson's moment-product partial correlation and multiple linear regressions were performed in SPSS v. 27 (Chicago Il USA). The significance was reported when p is below 0.05, but the higher significance levels, such as $p < 0.01$ and $p < 0.001$ were also indicated in this study. Regression analysis criteria were set at probability of F to enter ≤ 0.05 and probability of F to remove ≥ 0.10.

Results

Figure 1 showed that, currently, every population had very low magnitude of I_s because natural selection in each population has been reduced significantly by the advanced healthcare services. Worldwide, the I_s ranges between 0.01 (Iceland and Cyprus) and 0.58 (Burkina Faso), and the arithmetic mean is 0.09, which was approximately four times reduced from 100-150 years ago (I_s =0.22) [20]. In other word,

worldwide, human's capacity to survive natural selection without modern medicine has decreased approximately 4 times in the past 100-150 years.

Among the six (6) WHO Regions, the highest and lowest I_s (Darwin fitness) lied in Africa (I_s=0.023) and Europe (I_s = 0.02) [20].

Figure 2 noted that, inversely, I_s was in power correlation to dementia incidence rate in population of all ages (r=- 0.805, p<0.001, n=190) and 15-49 years old (r=- 0.857, p<0.001, n=190).

Table 1 showed that I_s was a significant predicting variable of dementia incidence rate in bivariate analyses. Worldwide, dementia incidence had significant and strong, but inverse, associations with I_s in both Pearson r (r=-0.827, p<0.001) and Spearman's rho (r= - 0.857, p<0.001). Additionally, in both data analysis models, dementia incidence was in significant and moderate, but positive, associations with ageing, GDP PPP and Urbanization respectively (r>0.500, p<0.001). Table 1 also presented the correlations between all variables.

Table 1 Pearson's r (above the diagonal) and Spearman rho (below the diagonal) between I_s (Darwin Fitness) and dementia incidence rates

Table 2 suggested that I_s was a significant risk factor for dementia incidence rate regardless of the competing effects of ageing, GDP PPP and urbanization. This was evidenced through examining the relationship between dementia incidence and I_s, ageing, GDP PPP and urbanization respectively which were alternated as the predicting variable while the other three variables were statistically kept constant. In the population of all ages, dementia incidence significantly correlated to Is (r= -0.429, p<0.001) and ageing (r= 0.278, p<0.001). However, dementia incidence correlated to I_s stronger than it to ageing on the edge of significant level (z=1.58, p=0.0571). In the population of all 15-49 years old, dementia incidence was in significant correlation to Is (r= 0.452, p<0.001), ageing (r= 0.126, p<0.001) and GDP PPP (r= 0.160, p<0.05) were in significant correlation to dementia incidence. Nonetheless, dementia incidence was in significantly stronger correlation to Is than to ageing (z=1.58, p< 0.001) and GDP PPP (z=2.98, p<0.001).

Table 2 Comparison of partial correlation coefficients between dementia incidence rate and each variable when the other three variables were kept statistically constant.

Table 3 presented that I_s was the only variable having the significant influence on dementia incidence in enter linear regression model for the populations of all ages (β= - 0.620, p<0.001) and 15-49 years old (β= - 0.679, p<0.001). In the subsequent stepwise multiple linear regression, I_s was selected as the variable which had the significant predicting effect on dementia incidence rates in the population of all ages (R^2=0.685) and population of 15-49 years old (R^2=0.738). For the population of 15-49 years old, GDP PPP was significantly correlated to dementia incidence rate (r=0.227, p<0.01) in enter linear model and was placed second to have the greatest influence on dementia incidence (increasing R^2 from 0.728 to 0.738)

in stepwise linear model. GDP PPP did not show significant predicting effect on dementia incidence in both enter and stepwise linear models.

Table 3 Multiple linear regression analyses to examine predictors of dementia incidence rate

Table 4 indicated that, regardless of population grouping criterion, I_s correlated to dementia incidence rate negatively, although the strength of correlation and significance level were different. One of highlights of the findings was that I_s was in stronger correlation to dementia incidence in developed population than in less developed population groupings. This is supported by the bivariate correlation between I_s and GDP PPP (r= 0.724 and 0.732 in Pearson's r and Spearman rho respectively, table 1)

Table 4 Correlations between I_s and dementia incidence rates in different country groupings

Discussion

Dementia is a growing public health concern owing to multiple aetiologies including population ageing. By assessing the dementia incidence rate data for 204 populations, this study suggested that decreasing Darwin Fitness (I_s) or less opportunity for natural selection is another major risk factor for dementia. It was also suggested that the developed populations have higher risk to develop dementia.

Dementia has strong genetics background which consist of those directly predisposing dementia and those from the comorbidities. The former source has been supported by the studies which concluded that Alzheimer [15] and frontotemporal [32–35] dementia are familial diseases. For instance, Slooter et al reported that about ¼ of the people aged 55+ may have genetic predisposition to develop dementia due to their family history of dementia involving their first-degree relatives [36]. Loy et al conducted a systematic review revealing that multiple genes involved in the onset of Alzheimer's disease, up to 70% of which may be inherited from a patient's parents [15]. A number of studies showed that about 20 - 40% of frontotemporal dementia patients who have a positive family history of frontotemporal diseases [32–35]. The strong genetics background of vascular dementia may be attributable to a group of heterogeneous cerebrovascular disorders leading to cognitive impairment [37–39]. For instance, vascular dementia is sometime considered as post-stroke dementia because it of the significant association between the nature of vascular dementia and stroke [40, 41], in particular ischemic stroke consisting of over of all strokes [42].

Dementia patients usually have a number of comorbidities which are non-communicable diseases. Averagely, the average number of comorbidities of a patient aged 65+ is four, but people without dementia have only two on average [43]. Most of the comorbidities have genetic predispositions which may be the potential triggers for dementia, such as hypertension [44], depressive disorders [45], obesity [46] and diabetes [47]. Therefore, genetic traits of these non-communicable diseases may be part of genetic predisposition of dementia as well.

Apparently, numerous genes predispose dementia, but their unbalanced interactions may also increase dementia incidence in multiple ways because of the pleiotropic effects of those genes. While research into genetic basis for dementia onset is still ongoing, the identification of specific genes predisposing specific dementia remain intriguing and intricate. Dementia genes and their variants are not devastatingly deleterious, and they have not created large potential for damage human survival [48]. Therefore, they will not be quickly eliminated by natural selection [49, 50]. In this study, the inverse correlation of I_s to dementia incidence rate suggested that I_s (Darwin Fitness) has been reduced by high level of healthcare services in modern society. This has made it possible for the frequencies of detrimental genetic backgrounds to accumulate in human population contributing to the increase of dementia incidence.

Globally, high level of healthcare service has relaxed the operation of natural selection (Darwin Fitness) on all populations in the past 100-150 years [13]. This was supported by the studies showing that the prevalence rates of a nasal septa and lacrimal bone defects increased because of the decreasing operation of natural selection [51]. This was also evidenced by the noticeable prevalence of phenylketonuria in population after it was accumulated for several generations with about 2% increase each [13, 52]. Recently, the accumulating effects of genetic traits of chronical diseases were tested on diabetes [10, 14], obesity [8, 9] and cancers [11]. The inverse correlation of I_s to dementia incidence is compatible with alteration of mutation-selection balance.

Without being reduced by modern healthcare service, natural selection could have had an ample opportunity to eliminate the dementia associated defective genetic background introduced by mutations through high fertility and high mortality [6, 13, 53–58]. However, dementia genes/mutations have been accumulated with the reduced natural selection because of low fertility and low mortality in the past 100-150 years [20]. Mathematically, dementia incidence rate could simply be doubled by generation if advanced healthcare services enable each individual to survive their reproduction period (Natural selection is reduced to zero.). However, natural selection is not relaxed down to zero in any population in the world, although it has been strongly relaxed leading to there I_s (Darwin fitness) varying between 0.01 and 0.58. Accordingly, the increase of dementia incidence rates is somewhat less than doubled, but varies between 421.6 (per 100,000) and 14.0 depending on population specific levels of dementia gene/mutation accumulation, living environment and their interactions [15, 16, 20]. Reduced natural selection has led to the increased presence of dementia associated comorbidities with genetic traits, such as diabetes [10, 14], obesity [8, 9] and cancers [11]. This has resulted that more and more people have survived their reproduction cycle (15-49 years) which allowed them to pass their detrimental genes/mutations of dementia and its comorbidities onto their next generations, thus increasing dementia presence.

Furthermore, worldwide, in particular in the developed populations, total fertility rate has been decreasing quickly, which has lessened biological variation in fertility [59]. A portion of this additional variation, however limited, would offer the opportunity for the natural selection [59]. The detrimental effects of decreasing fertility rate has been postulated as the leading risk factor for the increase of breast [31] and ovarian [30] cancer presence. It may be applicable to dementia incidence, but this could be another study.

Currently, the clinical treatment for dementia and their comorbidities only focuses on the control of symptoms [60], but not gene therapy to remove the dementia genes/mutation. Clinically, when dementia and its comorbidities are "cured", which only means that their symptoms, not their genetic background (genes/mutation), are under control or reversed. Currently or for next decades, healthcare services are impotent in removing the genetic traits of dementia and its comorbidities. Natural selection was supposed to function fully and remove the detrimental genes/mutations. However, it has been relaxed and cannot remove them all. The magnitude of removal depends on the extent to which their natural selection has been reduced. More specifically, populations with high level of healthcare services, their natural selection would be relaxed more and their dementia genes/mutations would be accumulated faster. This is supported by the dementia incidence rate increases with GDP PPP worldwide (Table 1) with special regards to in developed population groupings WHO European and American region, OECD and English-speaking populations (Table 4). One possible explanation may be that, worldwide, GDP increase has driven high level of healthcare services. The developed populations have been able to access healthcare services at higher level and for longer time, which has made them to escape natural selection more often and pass more detrimental genes onto their next generation [10, 13, 52].

Strengths and limitations

Little work has been done on dementia epidemiology. This may be because the onset rate is extremely low (93.70 per 100,000) which makes the presence not noticeable. The low presence rate of dementia would require large sample size which is unaffordable for capturing the incidence rate at the individual level or in laboratories. Ecological data are based on aggregated quantitative data which can zoom in the rare dementia presence 1,000,000 times, thus dementia presence becomes noticeable for correlating and identifying the potential contributing effects of dementia risk factors at population level. This necessity has been evidenced in other epidemiology studies of rare presence of non-communicable diseases (cancer [11, 30, 31] and Type 1 diabetes [10]).

The intrinsic limitations of ecological data should be considered when we are examining the public health implications of our results. 1) The results in this study only showed the correlation, not causation, between reduced natural selection and dementia incidence rate. 2) The relationship based on the ecological approach in this work are subject to ecological fallacy. Therefore, the protective role of less reduced natural selection may not always hold true for each individual, but it is possibly (p > 0.001) true at population level. 3) The population level data extracted for this study might be fairly crude. The IHME, WHO, United Nations and World Bank may have made some random errors when they are collecting and aggregating the data. 4) The opportunity for natural selection is only measured with respect to postnatal mortality, while gametic selection and intrauterine mortality are not included [61]. Regardless of the limitations of the ecological data, we have constantly showed that populations with more reduced natural selection had higher dementia incidence rate. The findings in this study may shed light for further longitudinal studies of human evolution at population level.

Conclusions

Worldwide, reduced natural selection may be another the significant contributor to the increasing incidence of dementia with special regard to developed population. It seems that, with ecological data, epidemiology studies may be the practical approach to identifying the potential causes of increasing dementia incidence. This may be helpful in addressing, or at least slowing down the presence of dementia at population level while modern healthcare services cannot operate effectively at the gene level yet.

Abbreviations

GDP PPP: Gross domestic product (at purchasing power parity)

I_{bs}: Biology State Index

I_s: A variant to measure Darwin Fitness (the magnitude of reduced natural selection) which was calculated with the formula, $I_s = (1-I_{bs})/I_{bs}$

Life e(65): Life expectancy at 65 years old

UN: United Nations

WHO: World Health Organization

IHME: Institute for Health Metrics and Evaluation

Declarations

Ethics approval and informed consent:

All the data supporting our findings in this paper were freely downloaded from the United Nation agencies' websites. No ethical approval or written informed consent for participation was required.

Consent for publication

Not applicable.

Availability of data and materials

The data sources have been described in the section of "Materials and Methods". All data for this study are freely available from the international organizations' official websites. The formal permission to use the data for non-commercial purpose is not necessary as it is compliant with the agency's public permission in their terms and conditions.

Competing interest

The authors declared that there is no conflict of interest.

Authors' contributions

WY and MH conceived the hypothesis and discussed with MH and RH for consolidation. WY extracted the data, and conducted analyses together with MH and RH before all the authors interpreted the analysis results. WY drafted the text with contributions from MH and RH; and all the authors reviewed, edited and approved the final manuscript for publishing.

Acknowledgments

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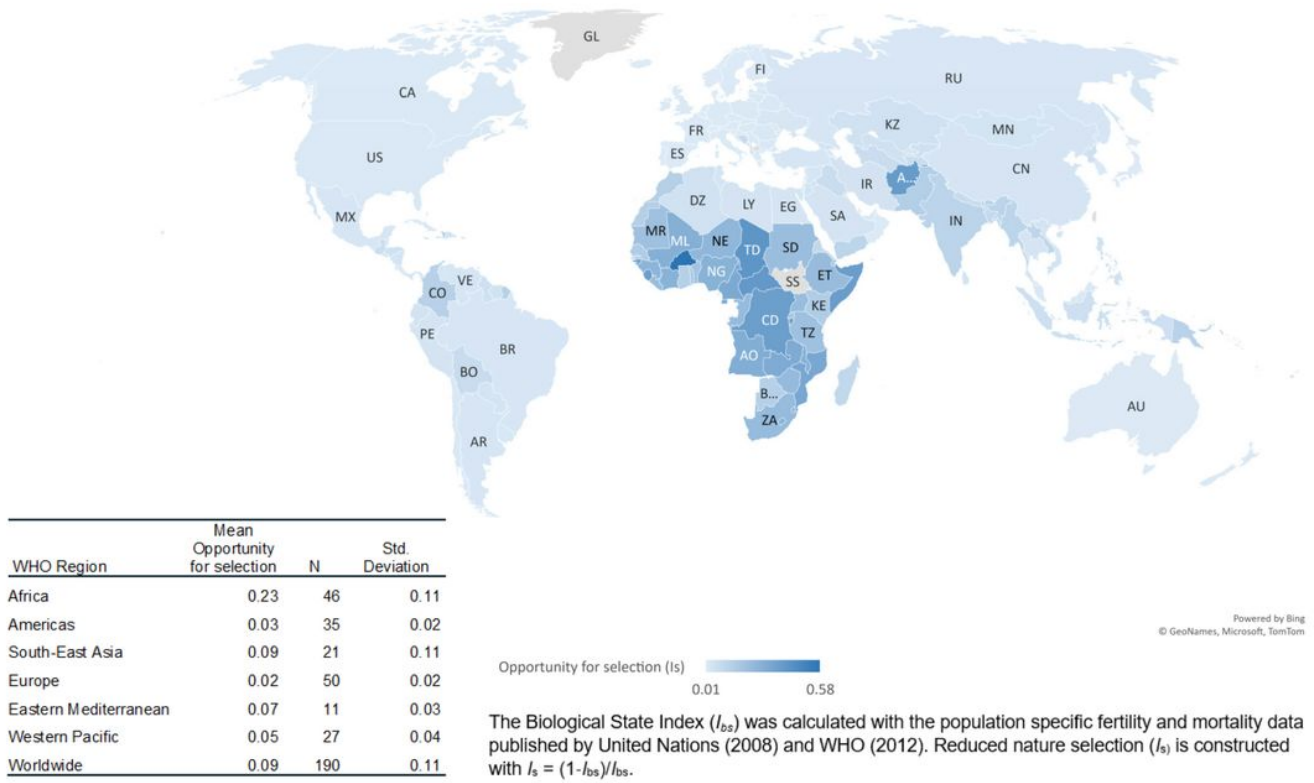
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Tables

Due to technical limitations, table 1, 2, 3 and 4 is only available as a download in the Supplemental Files section.

Figures

WHO Region	Mean Opportunity for selection	N	Std. Deviation
Africa	0.23	46	0.11
Americas	0.03	35	0.02
South-East Asia	0.09	21	0.11
Europe	0.02	50	0.02
Eastern Mediterranean	0.07	11	0.03
Western Pacific	0.05	27	0.04
Worldwide	0.09	190	0.11

Opportunity for selection (Is)

0.01   0.58

The Biological State Index (I_{bs}) was calculated with the population specific fertility and mortality data published by United Nations (2008) and WHO (2012). Reduced nature selection (I_s) is constructed with $I_s = (1-I_{bs})/I_{bs}$.

Figure 1

The magnitudes of Is (Darwin Fitness) in different regions

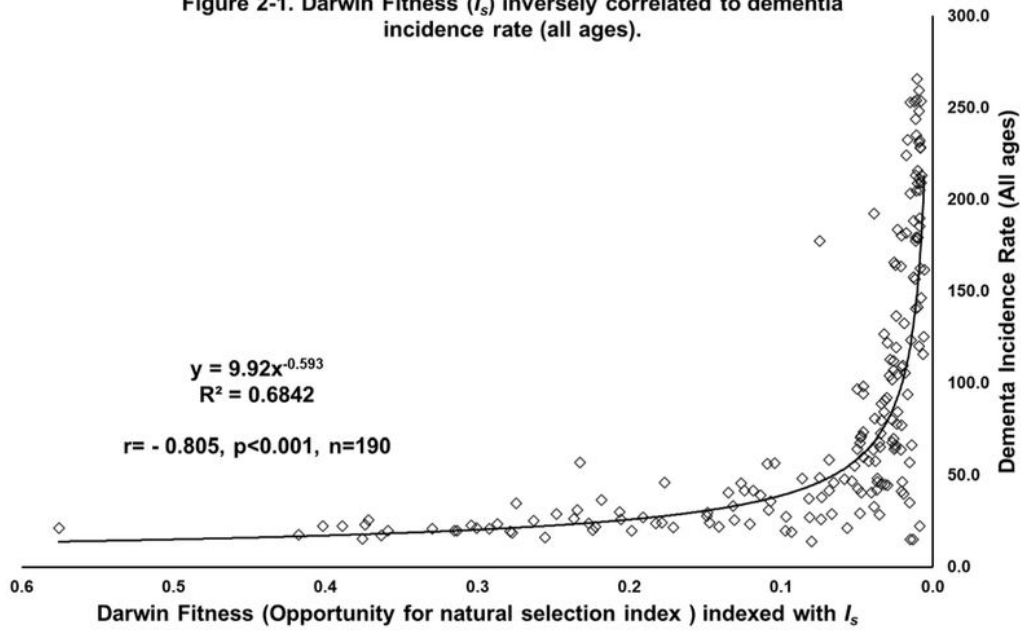Figure 2-1. Darwin Fitness (I_s) inversely correlated to dementia incidence rate (all ages).

$y = 9.92x^{-0.593}$
$R^2 = 0.6842$

$r = -0.805$, $p < 0.001$, $n = 190$

Figure 2-2. Darwin Fitness (I_s) inversely correlated to dementia incidence rate (15-49 years old)

$y = 1.3348x^{-0.219}$
$R^2 = 0.7336$

$r = -0.857$, $p < 0.001$, $n = 190$

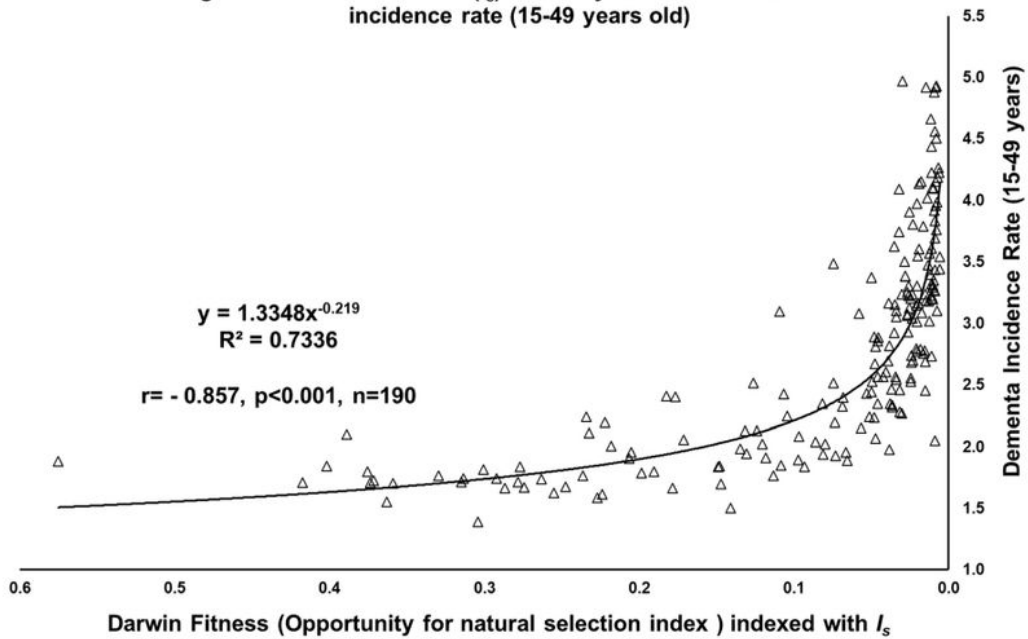## Figure 2

The relationships between Is (Darwin Fitness) and dementia incidence rates in populations of all ages and 15-49 years old

Supplementary Files

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- Tablesx4.rtf