Title: The relative roles of maternal survival and inter-personal violence as selection pressures on the persistence of Neanderthal hypercoagulability alleles in modern Europeans

Running title: Do Neanderthal *SELP* alleles protect against maternal peri-partum blood loss?

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Abstract

Background

Simoni *et al* (2016) reported variation in the frequency of Neanderthal alleles found in modern humans and argued that they may have provided an evolutionary advantage. One such allele is SNP rs3917862, associated with hypercoagulability. rs3917862 can be deleterious but can also help prevent blood loss. We investigated two possible selective pressure hypotheses for rs3917862 surviving to higher frequencies: deaths from interpersonal violent trauma and childbirth.

Results

Mortality data from modern hunter-gatherers models the living conditions and causes of death of humans and Neanderthals at the point of admixture. National census data indicates a positive correlation between presence of rs3917862 and decreased maternal mortality ratios. When maternal mortality ratio is modelled using GDP, births attended by skilled assistants and the presence of rs3917862, women are 0.1% more likely to die in childbirth in populations lacking rs3917862. Deaths due to violence show no correlation with rs3917862.

Conclusion

These findings challenge the idea that Neanderthal admixture has negatively impacted the overall health of modern humans. Maternal survival may have acted as a selective pressure for the persistence of hypercoagulability alleles in modern Europeans. Understanding the role of hypercoagulability in childbirth, and the role of rs3917862, could help to reduce maternal mortality ratios.

Keywords

Ancient DNA; maternal mortality; hypercoagulation; Neanderthal; adaptive introgression

Abbreviations

AICc	Akaike information criterion with correction for small sample sizes
F5	Coagulation Factor V
GDP	Gross domestic product
IVMR	Interpersonal violence per 100,000 deaths per year
MMR	Maternal mortality ratio
Protein C	Autoprothrombin IIA

42	SBA	Skilled birth assistance

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Introduction

The successful sequencing of the Neanderthal genome in 2010 revealed hitherto unsuspected levels of gene flow from Neanderthals into modern humans, providing researchers with the chance to examine the role this genetic admixture has had on modern human evolution (Green et al. 2010; Prüfer et al. 2014). Interbreeding between Neanderthals and anatomically modern humans has resulted in the genomes of modern humans (specifically non- Africans) containing between 1 and 4% Neanderthal DNA (Green et al. 2010; Wall et al. 2013; Prüfer et al. 2014). The overlap between anatomically modern humans and Neanderthals living outside Africa is estimated to have occurred approximately 45,000-41,000 years ago and lasted for between 2,600 and 5,400 years (Higham et al. 2014) although the overlap may have been for as much as 30,000 years with multiple pulses of admixture (Villanea & Schraiber 2019).

These interbreeding events have left a legacy of Neanderthal DNA which contributes to phenotypic variation in modern human populations. Simonti (Simonti et al. 2016) reported the contribution of common Neanderthal variants to over 1000 electronic health record-derived phenotypes in approximately 28,000 adults of European ancestry. A non-coding SNP of Neanderthal origin, rs3917862, located in an intron of P-selectin (*SELP*) on chromosome 1, was significantly associated with hypercoagulability. It had functional genomic marks suggestive of regulatory function and was significantly associated with the increased expression of *SELP* and *F5* in arteries which in turn increases risk of diseases related to hypercoagulability such as deep vein thrombosis and embolism (Simonti et al. 2016). The frequency of rs3917862 varies from 8.6% in CEU in Utah, 6.5% in Finnish in Finland, 3.2% in Columbians from Medellin, Columbia, and 1.2% in Bengali from Bangladesh, to 0.1% in Han Chinese in Beijing, and absent in African populations included in the 1000 Genomes Project (Pybus et al. 2014; Gibbs et al. 2015). However, high-resolution frequency data for this allele on a country-by-country basis is not currently available.

SELP codes for a cell adhesion protein, which is expressed on the endothelial cells and platelets that recruits leukocytes to injuries during inflammation (Simonti et al. 2016). *F5* codes for factor V, a coagulation cofactor which circulates in plasma and combines with factor X to activate prothrombin (Rallapalli et al. 2014). Rallapalli (Rallapalli et al. 2014) showed that the 11 coagulation factors in modern humans have undergone positive selection. Simonti concludes that there must have some advantage to the Neanderthal haplotype and that hypercoagulability would have been beneficial to early anatomically modern humans moving out of Africa (Simonti et al. 2016).

It is significant that rs3917862 has persisted given that hypercoagulability has been shown to have negative health impacts, potentially detrimentally affecting reproductive fitness. For example, hypercoagulability leads to increased risk of clot formation. Clot formation in turn can lead to venous thromboembolism – pulmonary embolism and deep vein thrombosis (Heit 2007). Malfunction of F5, a mutation called Factor V Leiden, increases thrombophilia and is found in approximately 20% of cases of venous thromboembolism (Rosendaal & Reitsma 2009). This mutation increases thrombophilia by causing amino acid substitution at one of the activated protein C cleavage sites of Factor V, rendering it resistant to activated protein C inactivation, and so leads to a reduction in the natural anticoagulant system, and enhances thrombin production (De Stefano & Leone 1995; Hooper & De Staercke 2002; Martinelli et al. 2010; Kyrle et al. 2010). Hypercoagulability, often used as a synonym for thrombophilia, increases the risk of venous thromboembolism. Increased risk of venous thromboembolism as a result of rs3917862 would, in turn, decrease the reproductive fitness carriers of this SNP, as it affects humans before and during their reproductive years.

However, hypercoagulability is not the only risk factor for venous thromboembolism. Old age, sedentism, obesity, air travel, oral contraceptives, surgery and cancer are all aspects of modern life that are also risk factors for venous thromboembolism (Rosendaal 2005; Prandoni et al. 2005; Heit 2007; Rosendaal & Reitsma 2009; Martinelli et al. 2010; Kyrle et al. 2010; Yang et al. 2012). Therefore, while hypercoagulability is a risk factor for contracting venous thromboembolism, modern life increases the occurrence of other predisposing factors, suggesting that hypercoagulability today is much more likely to contribute to the development of deep vein thrombosis or pulmonary embolism than it would have some 50,000 years ago. In situations where people were injured frequently (or otherwise dying from blood loss) hypercoagulability would be beneficial, as it would reduce the risk of death due to blood loss. It is these circumstances that are considered here, in order to determine which selective pressure could result in the persistence of introgressed Neanderthal hypercoagulability alleles in modern humans.

In order to understand the circumstances that would have resulted in hypercoagulability being advantageous, we must understand the living conditions of Neanderthals and anatomically modern humans approximately 50,000 years ago. Anthropologists have studied this in two ways: by observing the fossil record and through modelling (using modern hunter-gatherers as a model of likely living conditions before the advent of agriculture). Berger and Trinkaus (Berger & Trinkaus 1995) suggested that the frequency of trauma on Neanderthal skeletons is abnormally high and suggested that the trauma patterns on Neanderthal skeletons are similar to those seen in North American rodeo performers, as the injuries are predominantly to the upper body, which they argue might be evidence that Neanderthals came into close contact with large ungulates, presumably as a

result of close-quarter hunting. Trinkaus (Trinkaus 2012) later builds on this argument with the theory that Middle Palaeolithic spears were heavy and well suited for defence against carnivores and for ambush hunting. However, he also purports that the incidence of impact fractures on projectiles is suggestive of hunting at a distance (Trinkaus 2012). He offers two alternatives to hunting as the cause of these patterns of injury: interpersonal violence and foraging. Trinkaus (Trinkaus 2012) suggests that a number of the incidences of trauma show distinct signs of interpersonal violence: for example Zollikofer found evidence in the St Cesaire Neanderthal that the skull had been struck with a sharp implement, presumably during an act of interpersonal violence (Zollikofer et al. 2002). However, Underdown (Underdown 2006) argues that while Neanderthal trauma was common it was not abnormally high for hunter-gatherer populations and that patterns of trauma on Neanderthal skeletons are not related to hunting or interpersonal violence, suggesting instead that the trauma profile is most similar to that of the largely vegetarian Holocene Australian Aborigine population, and that the evidence of trauma is a result of accidents. Trinkaus (Trinkaus 2012) does suggest that a highly mobile foraging lifestyle could explain the predominantly upper body distribution of injuries, as injuries to the lower limbs would have prevented mobility and resulted in the injured being left behind in locations where remains would not have fossilised. Beier (Beier et al. 2018) analysed cranial trauma in 114 Neanderthal and 90 *Homo sapiens* skulls from the Upper Palaeolithic and showed that while males had a higher incidence of trauma than females there was no significant difference between the species. Importantly their work shows that it is not species that causes increased vulnerability to trauma but rather the risks posed by hunter-gathering in the Eurasian Palaeolithic.

Modern data sets from hunter-gatherers provide an insight into Neanderthal trauma and hominin mortality profiles. Marlowe (Marlowe 2005) suggests that there are several difficulties in using hunter-gatherer data in modelling hominin lifestyles before the advent of agriculture. Firstly, modern hunter-gatherers are likely to be a biased sample, as they exist only in marginal habitats not sought by agriculturalists. Secondly, it is highly unlikely that any of these forager groups exist entirely isolated from interaction with their agricultural neighbours, and so they are not living as our pre-agricultural ancestors were. However, Marlowe also makes the point that the ethnography of modern hunter-gatherers is the only way we can observe human behaviour in the absence of agriculture and so is the best proxy for the study of human behavioural and cultural evolution (Marlowe 2010). Once again, anthropologists are divided on what the hunter-gatherer evidence tells us about violence as a selective pressure. Hill and colleagues (HILL et al. 2007) use data from the Hiwi of Venezuela to suggest that high adult mortality rates in Neanderthal and early modern human populations are best explained by high levels of conspecific violence, as the Hiwi have lower rates of

infectious disease mortality, which more closely resembles the mortality profile of our Palaeolithic ancestors. If this is the case, then such high levels of interpersonal violence may have been a selective pressure for the persistence of hypercoagulability alleles. However, Wrangham and colleagues (Wrangham et al. 2006) suggest that mortality rates due to violence in forager and subsistence farming societies are highly variable. Indeed, they found that subsistence farming societies had higher rates of death due to interpersonal violence than hunter-gatherer societies (Wrangham et al. 2006). By this measure, violence would not be a consistent selective pressure. While anthropologists are largely divided on the presence and nature of violent and accidental deaths in Neanderthals and early modern humans, it is worth considering as a selective pressure for the persistence of hypercoagulability alleles in living Europeans.

Our hypothesis is that maternal mortality would present a more consistent selective pressure for the persistence of rs3917862. There are several pieces of evidence that suggest that the Neanderthal *SELP* SNP was maintained in the gene pool because it has advantages for maternal survival. Firstly, the main cause of death during childbirth in Africa and Asia is haemorrhaging (Ronsmans et al. 2006): indicating that in environments with limited healthcare blood loss is the most significant factor in maternal mortality. This is evidence to suggest that hypercoagulability plays a protective role against maternal haemorrhage during childbirth. Secondly, pregnancy is a risk factor for both hypercoagulability and venous thromboembolism (Rosendaal 2005; Heit 2007; Martinelli et al. 2010; Bourjeily et al. 2010). This hypercoagulability reduces the risk of excessive blood loss and death by haemorrhaging during delivery (Rosendaal 2005; Heit 2007; Martinelli et al. 2010; Bourjeily et al. 2010). Further evidence to suggest that hypercoagulability caused by rs3917862 might have persisted due to maternal mortality is that both *F5* and *SELP* are expressed in the placenta (Uhlén et al. 2015). While *SELP* RNA is expressed in many different tissues in the body, *F5* RNA is only expressed in the liver, gallbladder and placenta (Uhlén et al. 2015). Together this indicates that maternal mortality is a possible selective pressure for the persistence of rs3917862.

Materials and methods

Data collection

The data collected fall into four different categories: comparative causes of death for five modern hunter-gatherer groups, proportion of deaths caused by violence in fifteen hunter-gatherer populations, maternal mortality ratios (MMR) in different populations in Tanzania, and modern national census data.

Values for MMR, percentage of births attended by skilled birth assistants (SBA) and number of deaths due to interpersonal violence per 100,000 deaths per year (IVMR) were taken from the GBD 2015 SDG Collaborators (2016). GDP per capita data came from the World Bank (2016) for 188 countries. The presence or absence of Neanderthal allele rs3917862 was estimated from data from the 1000 Genomes Project which showed that the SNP was present in populations in Asia as well as Europe (Green et al. 2010; Aken et al. 2016). Allele frequency data is only available for 1000 Genomes populations (Gibbs et al. 2015) and per-country allele frequency data is not currently available.

Data analysis

Proportion of deaths from childbirth, interpersonal violence and accidents were expressed as percentages to ensure the deaths between populations were comparable, and were corrected for only females being at risk of maternal mortality. Hunter-gatherer mortality data (the percentage of deaths caused by childbirth, interpersonal violence and accidents) for five hunter-gatherer populations was visualised in bar plots using R (R Core Team 2013) (the San Ildefonso Agta (Early & Headland 1998), the Hiwi (HILL et al. 2007), the Hadza (Blurton Jones et al. 2002), the Ache (Hill & Hurtado 1996), and the Aka (Hewlett et al. 1986)). The number of deaths by interpersonal violence per 100,000 per year, as calculated by Kelly (Kelly 2013) was plotted as bar charts in order to compare the rates of violent deaths for fifteen hunter-gatherer populations (the Hadza (Marlowe 2010), the Andamanese (Keeley 1996), the Ju/'hoansi speaking !Kung (Lee 1979), the San Ildefonso Agta (Early & Headland 1998), the Gidjingali aborigine population (Hiatt 1965), the Tiwi (Keeley 1996), the Yahgan (Cooper 1917), the Yurok (Keeley 1996), the Casigurian Agta (Headland 1989), the Yulngu aborigine population (Keeley 1996), the Modoc (Keeley 1996), the Ache (Hill & Hurtado 1996), the Hiwi (HILL et al. 2007), the Piegan (Keeley 1996) and the Batek (Endicott & Endicott 2008) in (Kelly 2013)).

The authors calculated the MMR value for the Hadza (Blurton Jones 2016), and compared this data to the average MMR of Tanzania (Blurton Jones 2016), and the MMR values for the Haydom Lutheran Hospital in the Mbulu highlands (Olsen et al. 2002) and the Kilimanjaro Christian Medical Centre (Armon 1979).

The R package rworldmap (South 2011) was used to plot the MMR values and the rate of deaths due to interpersonal violence (IVMR) for 184 countries. R was used to plot the variables MMR, IVMR, SBA, GDP per capita and presence or absence of the allele rs3917862 against each other. Kendall's Rank Correlation Tau was used to determine variable correlation. R package ppcor (Kim 2015) was used to test the partial correlation of each pair of variables, with respect to the other variables, to

see whether any partial correlation was evident in the Kendall's Tau. R was then used to generate linear and polynomial regressions to model nine different potential explanations of the impact of SBA, allele presence and GDP on MMR. R package MuMIn (Bartón 2018) was used to calculate the AICc value for each of the nine models, giving the Akaike information criterion, which gives a measure of relative quality of a model. Adjusted AICc values were calculated by subtracting the lowest AICc value from the others. Models were then ranked in order of most to least effective. The best (most effective) model was visualised in three dimensions using the scatterplot3d package (Ligges & Mächler 2003). SBA was plotted against MMR, colouring the points by the presence or absence of rs3917862 in each population, and plotting the linear regression for those with the Neanderthal allele and those without. A Mann-Whitney U test was conducted to determine whether the two groups, those with the allele and those without, were significantly different in their central tendency. The R script used to produce these figures and results can be found in Supplementary material.

Results

The mortality profile data was used to compare the proportion of deaths due to interpersonal violence, childbirth (for females) and accidents for the San Ildefonso Agta, the Hiwi, the Hadza, the Ache and the Aka. Table 1 and supplementary figure 1 show that deaths due to interpersonal violence account for a higher percentage of deaths overall than either childbirth or accidents. However in the Agta, the Hadza and the Aka childbirth is responsible for a higher proportion of female deaths than violence. Deaths due to violence vary more widely between groups, while childbirth in this dataset is more consistent, accounting for between 0-6.7% of deaths.

We further examined the rate of deaths due to interpersonal violence using the homicide rate of fifteen hunter-gatherer groups. Table 2 shows that the rate of deaths due to interpersonal violence varies considerably between the different groups, with the lowest rate 1 death per 100,000 people per year (the Batek), and the highest over 1000 deaths due to homicide per 100,000 people per year.

We next considered the impact of hunter-gatherer lifestyle on death in childbirth, comparing the maternal mortality ratios of four populations in Tanzania: the Hadza, the Tanzanian national average, and two Tanzanian hospitals. Table 3 shows that maternal mortality is highest among the Hadza, which is higher than the national average. The two hospitals show MMR values much lower than the national average.

Considering the hypothesised role of Neanderthal variant rs3917862 in survival due to bloodloss-related trauma, we examined whether deaths due to interpersonal violence and childbirth corresponded with the presence of rs3917862 outside Africa. Figure 1 shows the MMR values for 184 countries, and the rate of deaths due to interpersonal violence for the same 184 countries. MMR correlates with the absence of the SNP in Africa, as the highest mortality rates are within Africa and in East Asia. Deaths due to interpersonal violence, in contrast, are highest in Russia, South America and parts of Africa.

Table 4 shows the result of Kendall's Tau. We tested the correlation between MMR and SBA, GDP per capita and presence/absence of the Neanderthal allele, and deaths due to interpersonal violence and SBA, GDP per capita and presence/absence of the Neanderthal allele. The correlations were significant for MMR and SBA, MMR and GDP per capita, and MMR and the presence/absence of the Neanderthal allele. For deaths due to interpersonal violence, correlations with GDP per capita and SBA were significant, however deaths due to interpersonal violence did not significantly correlate with presence/absence of the Neanderthal allele. To determine whether any of these correlations were a result of correlation with other unaccounted-for variables, rather than as a result of direct correlation, we ran partial correlation tests, again using Kendall's Tau. Table 5 shows the Tau and p-values for each pair of variables, controlling for each other variable in turn. Correlations were still significant for all pairs of variables with MMR, however, deaths due to interpersonal violence no longer correlated with skilled birth assistance when controlling for GDP per capita. Therefore deaths due to interpersonal violence correlated only with GDP per capita. As deaths due to interpersonal violence did not significantly correlate with presence/absence of rs3917862, we did not model this relationship further.

To examine the correlation between MMR and the presence of rs3917862 further, we modelled MMR using SBA, GDP, presence/absence of rs3917862 and log(GDP) as predictors. Table 6 shows the regression coefficients and p-value for each coefficient for all of the models. Table 7 shows the adjusted R^2 value for each of the nine models, the AICc values for each model, the Δ AICc and finally the models are ranked from best to worst, in order to determine which model best explains the variation in MMR. For this data the best model is:

$$MMR = 970.52 - 522SBA - 104.37allele - 34.47log(GDP)$$

which has an R2 value of 0.7277, and uses SBA, presence/ absence of rs3917862 (*allele*) and the log of GDP per capita to explain the variation in MMR. This equation suggests that those who come from

a population with the Neanderthal allele rs3917862 have 104.37/100,000 or approximately 0.1% lower MMR, although this does not imply that the difference is caused by the presence of rs3917862

We visualised the best model using a three-dimensional scatterplot, in order to better understand the relationship between the different predictors. Figure 2 shows that MMR is generally lower, and SBA generally higher for populations with the Neanderthal allele as compared to those without, while GDP has little visible correlation. As GDP did not visibly cluster with higher or lower rates of maternal mortality in our data, we plotted a two-dimensional scatter plot of SBA and MMR. Figure 3 shows that there is a difference in MMR between those populations that have the Neanderthal variant and those who do not. Indeed, when not accounting for log(GDP) it appears a though there is a difference of 125.3 deaths in childbirth per 100,000 live births between countries that have rs3917862 represented and those who do not. In order to further investigate this difference, we subdivided the data into the nations that have the Neanderthal SNP and those who do not. We tested the difference in the central tendency of these two subsets using a Mann-Whitney Wilcoxon test, in order to determine whether these groups were significantly different. The test returned a p-value of <2.2e-16, which would suggest that the countries with rs3917862 are statistically significantly different in the central tendency of the distribution of MMR values.

Discussion

Intronic Neanderthal SNP Rs391782 appears to have a regulatory function, resulting in increased expression of *SELP* and *F5*, which in turn results in a hypercoagulability phenotype. Using modern hunter-gatherer data, we examined what selective pressures pre-agricultural lifestyles would have exerted to potentially cause the persistence of the hypercoagulability phenotype. The heightened risk of maternal morbidity and mortality is well established (Ortner 1998)and this effect is increased in the developing world where access to medical care can be severely reduced. In high income countries the risk of maternal death is 1 in 3,3300 while in low income it is 1 in 41 (WHO 2015). Prehistoric human populations would similarly have faced a much greater risk of death from child birth than those in the modern developed world. Death during pregnancy can occur from a wide range of complications such as infection, eclampsia, obstructed labour and haemorrhage but it is largely impossible to measure the relative risk of these in archaeological populations (Ortner 2003). Yet in modern data haemorrhage is the leading cause of maternal mortality accounting for 27% of deaths (Say et al. 2014). However, pregnancy and life threatening complications arising from it are extremely hard to detect in the archaeological record via skeletal evidence. Palaeopathologists have suggested that changes to the pubic bone adjacent to the pubic symphysis in the form of pitting and erosion are diagnostic of parturition (e.g. (Stewart 1968) and (Gilbert & McKern 1973)) but there

remains little definitive evidence to support this association (Ortner 2003). More recent analysis in Denmark (Poulsen et al. 2001) and Norway (Turner-Walker et al. 2001; Mays et al. 2006) linked significant decrease in bone mineral density in young Danish mediaeval female skeletons with stress caused by pregnancy and lactation. They argue that this increase in physiological stress would have increased the risk of mortality. However, Agarwal (Agarwal et al. 2018) highlights that the while skeletal change could be attributed to pregnancy, patterns of geographical variation must be considered and in very northerly latitudes the impact of reproductive bone loss could be greatly compounded by lack of vitamin D due to low levels of UV exposure. Ultimately pregnancy is extremely difficult to identify in the archaeological record yet the pressures faced by populations in the past are likely to be similar, if not much greater, than those faced by women in the developing world. The data presented here were insufficient to prove any single selective pressure was responsible for the persistence of rs3917862; however, we show that deaths due to interpersonal violence were more frequent, but much less consistent, than deaths as a result of childbirth. This suggests that childbirth-related trauma and deaths are an evolutionarily more consistent selection pressure which could drive selection for hypercoagulability phenotypes, and examines a problem that is very difficult to assess in the archaeological record alone.

National census data for death due to interpersonal violence and childbirth was used to examine whether the Neanderthal allele rs3917862 was associated with either cause of mortality. Deaths due to interpersonal violence did not correlate with the presence or absence of the Neanderthal SNP, suggesting that deaths due to interpersonal violence are not an adequate hypothesis to explain the persistence of this hypercoagulability allele. Death in childbirth, by contrast, did correlate with the presence or absence of rs3917862, even when taking into consideration that both correlate with GDP and with percentage of births attended by skilled birth assistants. In modelling the causes of MMR, the best model was an additive model including three variables, GDP, percentage of births attended by skilled birth assistants and presence or absence of the Neanderthal SNP. Even with three variables, the presence or absence of the allele is significant in best explaining variation in maternal mortality in our model. Populations with rs3917862 experienced 0.1% fewer deaths during childbirth than populations without the allele. Together with the fact that haemorrhaging is still the biggest cause of death in Africa and Asia (Ronsmans et al. 2006), *SELP* and F5 are expressed in the placenta and that pregnancy is already associated with increased coagulation in order to prepare the body for childbirth, it remains possible that rs3917862 has persisted as a result of selection for adaptations which reduces deaths due to blood loss during childbirth. However, other factors not captured in the model may also correlate with the presence of rs3917862 and rs3917862 may be acting as a proxy for other factors.

Limitations of this study

While these findings are undoubtedly valuable in generating new hypotheses to understand the persistence of hypercoagulability alleles in modern Europeans, there are a number of caveats that must be considered. Firstly, country-level data for the frequency of rs3917862, which ranges from 0 0.1-8.5% outside Africa for 1000 Genomes populations, is only available for a limited number of countries and is taken from sometimes modest population sample sizes. Any study of this kind must consider the issue of the binary nature of the presence or absence of the allele which was recorded as a compromise to deal with missing data. Here we have assumed that, when there is no direct value available on ensemble.org or SNPdb, the Neanderthal allele is present outside Africa, and absent in Africa, as is typical in almost all Neanderthal admixture studies (Green et al. 2010; Prüfer et al. 2014; Sankararaman et al. 2016). However, it is possible that this binary is representative of some other difference between Africa and outside Africa other than GDP and skilled birth assistance that has not been taken into account. Secondly, the census data set is at national level, and does not allow further break down of the data to ethnic or linguistic groups, which means that estimations of presence/absence of rs3917862 may be further affected by within-country, between-group variation. For example, within China only Han Chinese are known to carry rs3917862, but this was recorded in this study as the entirety of China having the presence of the allele (Aken et al. 2016). Thirdly, the mortality data subset gives no indication of what the specific cause of death was, other than the categories of interpersonal violence or death in childbirth. This increases the noise of the dataset: for example, we do not know the proportion of deaths in each group caused by haemorrhaging, infection, hypertension or other direct or indirect causes. The measure of births attended by skilled birth assistants is also likely to be inflated, as this is census data, and births are more likely to be registered if they are attended by a skilled birth assistant. With these caveats in mind, the presence of Neanderthal allele rs3917862 is still associated with increased maternal survival during childbirth, and childbirth-related blood loss and trauma/mortality and would have acted as a far stronger selective pressure than that presented by stochastic incidences of interpersonal violence. The problems inherent in identifying pregnancy related changes to the skeleton or skeletal markers of obstetric complications has created a false picture of how selection would have operated on populations in the past. The method adopted here allows us to actively generate new hypotheses that ameliorate the issues presented by the skeletal data.

Ultimately our results indicate a new hypothesis for the persistence of hypercoagulability alleles and thus point to areas for further research; and we provide tentative evidence to suggest that maternal

survival could have acted as a selection pressure for the persistence of hypercoagulability alleles in modern Europeans. Large population studies or commercial providers with extensive genotype and phenotype data such as ALSPAC (Fraser et al. 2013), the UKBiobank (Sudlow et al. 2015) or 23andme (Day et al. 2018) may be productive in examining the relationship between hypercoagulability alleles and birth outcomes in women with linked phenotype and genotype data, or studies specifically addressing the genetics of blood related traits, such as INTERVAL (Di Angelantonio et al. 2017).

Conclusion

These findings add depth to our understanding of the impact of Neanderthal admixture on modern human health and highlight the under-appreciated importance of the risks (and thus selective pressures) associated with childbirth in human evolution. Understanding the selective pressures that may have resulted in the persistence of rs3917862 in modern humans can help improve modern healthcare, and draw further attention to haemorrhaging as a still-significant risk for people in Africa and Asia, while hypertension and venous thromboembolism are a risk for women world-wide.

Quick summary

We hypothesise that Neanderthal *SELP* SNP rs3917862 is more likely to have been maintained in human populations to prevent maternal death due to peri-partum blood loss, than to prevent blood loss due to trauma and interpersonal violence, and present statistical models of the association between the SNP and these causes of death.

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Declaration of interest statement

The authors declare no relevant conflicts of interest.

References

Agarwal S, Kovilam O, Agrawal DK. 2018. Vitamin D and its impact on maternal-fetal outcomes in pregnancy: A critical review. Crit Rev Food Sci Nutr [Internet]. [cited 2019 Mar 28]; 58:755–769. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27558700

Aken BL, Ayling S, Barrell D, Clarke L, Curwen V, Fairley S, Fernandez Banet J, Billis K, García Girón C, Hourlier T, et al. 2016. The Ensembl gene annotation system. Database [Internet]. [cited 2019 Feb 5];

2016:baw093. Available from: https://academic.oup.com/database/article-lookup/doi/10.1093/database/baw093

Di Angelantonio E, Thompson SG, Kaptoge S, Moore C, Walker M, Armitage J, Ouwehand WH, Roberts DJ, Danesh J, Di Angelantonio E, et al. 2017. Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomised trial of 45 000 donors. Lancet [Internet]. [cited 2019 Mar 27]; 390:2360–2371. Available from: https://www.sciencedirect.com/science/article/pii/S0140673617319281

Armon PJ. 1979. Maternal deaths in the kilimanjaro region of tanzania. Trans R Soc Trop Med Hyg [Internet]. [cited 2019 Feb 5]; 73:284–288. Available from: https://academic.oup.com/trstmh/article-lookup/doi/10.1016/0035-9203(79)90083-X

Bartón K. 2018. MuMIn: Multi-Model Inference. R Packag version 1404 https//CRANR-project.org/package=MuMIn Bates,.

Beier J, Anthes N, Wahl J, Harvati K. 2018. Similar cranial trauma prevalence among Neanderthals and Upper Palaeolithic modern humans. Nature [Internet]. [cited 2018 Nov 15]; 563:686–690. Available from: http://www.nature.com/articles/s41586-018-0696-8

Berger TD, Trinkaus E. 1995. Patterns of Trauma among the Neandertals. J Archaeol Sci [Internet]. [cited 2014 Aug 7]; 22:841–852. Available from: http://www.sciencedirect.com/science/article/pii/0305440395900136

Blurton Jones N. 2016. Demography and evolutionary ecology of hadza hunter-gatherers. [place unknown]; [cited 2019 Feb 5]. Available from: https://books.google.co.uk/books?hl=en&lr=&id=oh90CwAAQBAJ&oi=fnd&pg=PR13&dq=Demography+and+Evolutionary+Ecology+of+Hadza+Hunter-+Gatherers.&ots=1caFDXwP3D&sig=S2YImIdSVimB-GVttmbvPphY3_w

Blurton Jones NG, Hawkes K, O'Connell JF. 2002. Antiquity of postreproductive life: Are there modern impacts on hunter-gatherer postreproductive life spans? Am J Hum Biol [Internet]. [cited 2019 Feb 5]; 14:184–205. Available from: http://doi.wiley.com/10.1002/ajhb.10038

Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. 2010. Pulmonary embolism in pregnancy. Lancet (London, England) [Internet]. [cited 2019 Feb 5]; 375:500–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19889451

Cooper JM. 1917. Analytical and critical bibliography of the tribes of Tierra del Fuego and adjacent territory. BAE Bull. 63:1881–1949.

Day F, Karaderi T, Jones MR, Meun C, He C, Drong A, Kraft P, Lin N, Huang H, Broer L, et al. 2018. Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria.Cotsapas C, editor. PLOS Genet [Internet]. [cited 2019 Mar 27]; 14:e1007813. Available from: http://dx.plos.org/10.1371/journal.pgen.1007813

Early J, Headland T. 1998. Population dynamics of a Philippine rain forest people: The San Ildefonso Agta.

Endicott K, Endicott K. 2008. The headman was a woman: The gender egalitarian Batek of Malaysia. [place unknown].

Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, et al. 2013. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol [Internet]. [cited 2019 Mar 27]; 42:97–110. Available from: https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/dys066

Gibbs RA, Boerwinkle E, Doddapaneni H, Han Y, Korchina V, Kovar C, Lee S, Muzny D, Reid JG, Zhu Y, et al. 2015. A global reference for human genetic variation. Nature [Internet]. [cited 2019 Mar 27]; 526:68–74. Available from: http://www.nature.com/articles/nature15393

Gilbert BM, McKern TW. 1973. A method for aging the femaleOs pubis. Am J Phys Anthropol [Internet]. 38:31–38. Available from: http://doi.wiley.com/10.1002/ajpa.1330380109

Green RE, Krause J, Briggs AW, Maricic T, Stenzel U, Kircher M, Patterson N, Li H, Zhai W, Fritz MH-Y, et al. 2010. A draft sequence of the Neandertal genome. Science [Internet]. [cited 2014 May 24]; 328:710–22. Available from: http://www.sciencemag.org/content/328/5979/710.full

Headland TN. 1989. Population decline in a Philippine Negrito hunter-gatherer society. Am J Hum Biol [Internet]. [cited 2019 Feb 5]; 1:59–72. Available from: http://doi.wiley.com/10.1002/ajhb.1310010111

Heit JA. 2007. Thrombophilia: common questions on laboratory assessment and management. Hematol Am Soc Hematol Educ Progr [Internet]. [cited 2019 Feb 5]; 2007:127–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18024620

Hewlett BS, Koppel JMH Van De, Koppel M van de. 1986. Causes of Death among Aka Pygmies of the Central African Republic. In: African Pygmies [Internet]. [place unknown]; [cited 2019 Feb 5]; p. 45–63. Available from: https://scholar.google.co.uk/scholar?hl=en&as_sdt=0%2C5&q=Causes+of+Death+among+Aka+Pygmies+of+the+Central+African+Republic.&btnG=

Hiatt L. 1965. Kinship and conflict: a study of an Aboriginal community in northern Arnhem Land. [place unknown].

Higham T, Douka K, Wood R, Ramsey CB, Brock F, Basell L, Camps M, Arrizabalaga A, Baena J, Barroso-Ruíz C, et al. 2014. The timing and spatiotemporal patterning of Neanderthal disappearance. Nature [Internet]. [cited 2014 Aug 20]; 512:306–309. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25143113

Hill K, Hurtado A. 1996. Ache life history: The ecology and demography of a foraging people [Internet]. [place unknown]: AldineTransaction; [cited 2019 Feb 5]. Available from: https://content.taylorfrancis.com/books/download?dac=C2017-0-45441-4&isbn=9781351329248&format=googlePreviewPdf

HILL K, HURTADO A, WALKER R. 2007. High adult mortality among Hiwi hunter-gatherers: Implications for human evolution. J Hum Evol [Internet]. [cited 2016 Oct 31]; 52:443–454. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0047248406002193

Hooper WC, De Staercke C. 2002. The relationship between FV Leiden and pulmonary embolism. Respir Res [Internet]. [cited 2019 Feb 5]; 3:8. Available from: http://respiratory-research.biomedcentral.com/articles/10.1186/rr180

Keeley LH. 1996. War before Civilization [Internet]. [place unknown]; [cited 2019 Feb 5]. Available from: https://books.google.co.uk/books?hl=en&lr=&id=Q8MHKQrFeEEC&oi=fnd&pg=PA3&dq=Keeley,+L.,1996.+War+Before+Civilization&ots=jd-UBJ3edB&sig=KELI_DRKnht_ymPjbnDHsX7fGQI

Kelly RL. 2013. The Lifeways of Hunter-Gatherers [Internet]. [place unknown]; [cited 2019 Feb 5]. Available from: https://books.google.co.uk/books?hl=en&lr=&id=CDAWBQAAQBAJ&oi=fnd&pg=PR11&dq=The+Lifeways+of+Hunter-Gatherers:+The+Foraging+Spectrum.+kelly&ots=uriwOOKXIj&sig=uBxkDOVwI69Pnxjqmk0rQrj0T9E

Kim S. 2015. ppcor: An R Package for a Fast Calculation to Semi-partial Correlation Coefficients. Commun Stat Appl Methods [Internet]. [cited 2019 Feb 5]; 22:665–674. Available from: http://www.csam.or.kr/journal/view.html?doi=10.5351/CSAM.2015.22.6.665

Kyrle PA, Rosendaal FR, Eichinger S. 2010. Risk assessment for recurrent venous thrombosis. Lancet (London, England) [Internet]. [cited 2019 Feb 5]; 376:2032–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21131039

Lee R. 1979. The !Kung San: men, women and work in a foraging society. [place unknown]: Cambridge.

Ligges U, Mächler M. 2003. scatterplot3d - An R Package for Visualizing Multivariate Data. J Stat Softw [Internet]. [cited 2019 Feb 5]; 8:1–20. Available from: http://www.jstatsoft.org/v08/i11/

Marlowe FW. 2005. Hunter-gatherers and human evolution. Evol Anthropol [Internet]. [cited 2016 Oct 31]; 14:54–67. Available from: http://doi.wiley.com/10.1002/evan.20046

Marlowe FW. 2010. The Hadza: hunter-gatherers of Tanzania [Internet]. [place unknown]; [cited 2019 Feb 5]. Available from: https://books.google.co.uk/books?hl=en&lr=&id=8p-AG8cqCJwC&oi=fnd&pg=PT6&dq=The+Hadza:+hunter-gatherers+of+Tanzania+Authors+Frank+Marlowe&ots=jAAZmywpZq&sig=F0p4r7CbpbmT5eZHoVWETVG4_GE

Martinelli I, Bucciarelli P, Mannucci PM. 2010. Thrombotic risk factors: Basic pathophysiology. Crit Care Med [Internet]. [cited 2019 Feb 5]; 38:S3–S9. Available from: https://insights.ovid.com/pubmed?pmid=20083911

Mays S, Turner-Walker G, Syversen U. 2006. Osteoporosis in a population from medieval Norway. Am J Phys Anthropol [Internet]. [cited 2019 Mar 28]; 131:343–351. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16634046

Olsen BE, Hinderaker SG, Lie RT, Bergsjø P, Gasheka P, Kvåle G. 2002. Maternal mortality in northern rural Tanzania: Assessing the completeness of various information sources. Acta Obstet Gynecol Scand [Internet]. [cited 2019 Feb 5]; 81:301–307. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11952458

Ortner D. 1998. Male-female immune reactivity and its implications for interpreting evidence in human skeletal paleopathology. In: Sex Gend paleopathological Perspect [Internet]. [place unknown]: Cambridge University Press; [cited 2019 Mar 28]; p. 79–92. Available from: https://books.google.co.uk/books?hl=en&lr=&id=2Zhi_2-zFQwC&oi=fnd&pg=PA79&dq=Male-female+immune+reactivity+and+its+implications+for+interpreting+evidence+in++human+skeletal+paleopathology&ots=JKa34n0O20&sig=KN7h-wguhygfS-MXtNV0TIoTf1g

Ortner DJ. 2003. Identification of pathological conditions in human skeletal remains. [place unknown]: Academic Press.

Poulsen L., Qvesel D, Brixen K, Vesterby A, Boldsen J. 2001. Low bone mineral density in the femoral neck of medieval women: a result of multiparity? Bone [Internet]. [cited 2019 Mar 28]; 28:454–458.

526 Available from: https://www.sciencedirect.com/science/article/pii/S8756328201004070

527 Prandoni P, Falanga A, Piccioli A. 2005. Cancer and venous thromboembolism. Lancet Oncol
528 [Internet]. [cited 2019 Feb 5]; 6:401–410. Available from:
529 https://www.sciencedirect.com/science/article/pii/S1470204505702072?via%3Dihub

530 Prüfer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, Heinze A, Renaud G, Sudmant PH,
531 de Filippo C, et al. 2014. The complete genome sequence of a Neanderthal from the Altai Mountains.
532 Nature [Internet]. [cited 2014 May 27]; 505:43–49. Available from:
533 http://www.nature.com/articles/nature12886

534 Pybus M, Dall'Olio GM, Luisi P, Uzkudun M, Carreño-Torres A, Pavlidis P, Laayouni H, Bertranpetit J,
535 Engelken J. 2014. 1000 Genomes Selection Browser 1.0: a genome browser dedicated to signatures
536 of natural selection in modern humans. Nucleic Acids Res [Internet]. [cited 2019 Mar 27]; 42:D903–
537 D909. Available from: https://academic.oup.com/nar/article-lookup/doi/10.1093/nar/gkt1188

538 R Core Team. 2013. R: A language and environment for statistical computing. Vienna R Foudation
539 Stat Comput.

540 Rallapalli PM, Orengo CA, Studer RA, Perkins SJ. 2014. Positive Selection during the Evolution of the
541 Blood Coagulation Factors in the Context of Their Disease-Causing Mutations. Mol Biol Evol
542 [Internet]. [cited 2019 Feb 5]; 31:3040–3056. Available from:
543 https://academic.oup.com/mbe/article-lookup/doi/10.1093/molbev/msu248

544 Ronsmans C, Graham WJ, Lancet Maternal Survival Series steering group. 2006. Maternal mortality:
545 who, when, where, and why. Lancet (London, England) [Internet]. [cited 2019 Feb 5]; 368:1189–200.
546 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17011946

547 Rosendaal FR. 2005. Venous thrombosis: the role of genes, environment, and behavior. Hematol Am
548 Soc Hematol Educ Progr [Internet]. [cited 2019 Feb 5]; 2005:1–12. Available from:
549 http://www.ncbi.nlm.nih.gov/pubmed/16304352

550 Rosendaal FR, Reitsma PH. 2009. Genetics of venous thrombosis. J Thromb Haemost [Internet].
551 [cited 2019 Feb 5]; 7:301–304. Available from: http://doi.wiley.com/10.1111/j.1538-
552 7836.2009.03394.x

553 Sankararaman S, Mallick S, Patterson N, Reich D. 2016. The Combined Landscape of Denisovan and
554 Neanderthal Ancestry in Present-Day Humans. Curr Biol [Internet]. [cited 2017 Feb 23]; 26:1241–7.
555 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27032491

556 Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, Gülmezoglu AM, Temmerman M, Alkema

L. 2014. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Heal [Internet]. [cited 2019 Mar 28]; 2:e323–e333. Available from: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(14)70227-X/fulltext

Simonti CN, Vernot B, Bastarache L, Bottinger E, Carrell DS, Chisholm RL, Crosslin DR, Hebbring SJ, Jarvik GP, Kullo IJ, et al. 2016. The phenotypic legacy of admixture between modern humans and Neandertals. Science [Internet]. [cited 2018 Aug 17]; 351:737–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26912863

South A. 2011. rworldmap: a new R package for mapping global data. R J.

De Stefano V, Leone G. 1995. Resistance to activated protein C due to mutated factor V as a novel cause of inherited thrombophilia. Haematologica [Internet]. [cited 2019 Feb 5]; 80:344–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7590506

Stewart T. 1968. Identification of the scars of parturition in the skeletal remains of females. In: Pers Identif mass disasters [Internet]. [place unknown]; [cited 2019 Mar 28]; p. 127–137. Available from: https://scholar.google.co.uk/scholar?hl=en&as_sdt=0%2C5&q=+Identification+of+the+Scars++of+Parturition+in+the+Skeletal+Remains+of+Females.&btnG=

Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. 2015. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLOS Med [Internet]. [cited 2019 Mar 27]; 12:e1001779. Available from: https://dx.plos.org/10.1371/journal.pmed.1001779

Trinkaus E. 2012. Neandertals, early modern humans, and rodeo riders. J Archaeol Sci [Internet]. [cited 2019 Feb 5]; 39:3691–3693. Available from: https://www.sciencedirect.com/science/article/pii/S030544031200297X

Turner-Walker G, Syversen U, Mays S. 2001. The Archaeology of Osteoporosis. Eur J Archaeol [Internet]. [cited 2019 Mar 28]; 4:263–269. Available from: http://eja.sagepub.com/cgi/doi/10.1177/146195710100400207

Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, et al. 2015. Tissue-based map of the human proteome. Science (80-) [Internet]. [cited 2019 Feb 5]; 347:1260419–1260419. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25613900

Underdown SJ. 2006. A comparative approach to understanding neanderthal trauma. Period Biol [Internet]. [cited 2019 Feb 5]; 108:485–493. Available from:

http://www.scopus.com/inward/record.url?eid=2-s2.0-33746972486&partnerID=tZOtx3y1

Villanea FA, Schraiber JG. 2019. Multiple episodes of interbreeding between Neanderthal and modern humans. Nat Ecol Evol [Internet]. [cited 2019 Feb 5]; 3:39–44. Available from: http://www.nature.com/articles/s41559-018-0735-8

Wall JD, Yang MA, Jay F, Kim SK, Durand EY, Stevison LS, Gignoux C, Woerner A, Hammer MF, Slatkin M. 2013. Higher levels of neanderthal ancestry in East Asians than in Europeans. Genetics [Internet]. [cited 2019 Feb 5]; 194:199–209. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10757768

WHO. 2015. Global Health Observatory (GHO): Trends in maternal mortality 1990-2015. UNICEF, UNFPA, World Bank Group and the United Nations Population Division [Internet]. [place unknown]; [cited 2019 Mar 28]. Available from: https://apps.who.int/iris/handle/10665/194254

Wrangham RW, Wilson ML, Muller MN. 2006. Comparative rates of violence in chimpanzees and humans. Primates [Internet]. [cited 2019 Feb 5]; 47:14–26. Available from: http://link.springer.com/10.1007/s10329-005-0140-1

Yang G, Staercke C De, Hooper WC. 2012. The effects of obesity on venous thromboembolism: A review. Open J Prev Med [Internet]. [cited 2019 Feb 5]; 02:499–509. Available from: http://www.scirp.org/journal/doi.aspx?DOI=10.4236/ojpm.2012.24069

Zollikofer CPE, Ponce De Leon MS, Vandermeersch B, Leveque F. 2002. Evidence for interpersonal violence in the St. Cesaire Neanderthal. Proc Natl Acad Sci U S A [Internet]. [cited 2019 Feb 5]; 99:6444–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11972028

609 Table 1: percentages of deaths attributable to childbirth (female only), violence and accident in five
610 hunter-gatherer populations

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Population	Continent	Percentage of female deaths in childbirth	Percentage of male deaths in violence	Percentage of female deaths in violence	Percentage of male deaths due to accident	Percentage of female deaths due to accident
San Ildefonso Agta	Asia	9.9%	6.7%	0.6%	6.1%	0%
Hiwi	South America	7.9%	32.2%	28.6%	8.9%	11.1%
Hadza	Africa	14.7%	7.3%	2.9%	2.4%	0%
Ache	South America	1.8%	51.8%	60.5%	17.3%	7.4%
Aka	Africa	4.8%	0.5%	0%	6.5%	3.8%

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614 Table 2: The homicide rates of fifteen hunter-gatherer groups from five
615 continents

Population	Continent	Homicide rate, per 100,000, per year
Hadza	Africa	6.6
Andamanese	Asia	20
Ju/'hoansi	Africa	42
San Ildefonso Agta	Asia	129
Gidjingali	Australia	148
Tiwi	Australia	160
Yaghan	South America	169
Yurok	North America	240
Casiguran Agta	Asia	326
Yolngu	Australia	330
Modoc	North America	450
Ache	South America	500
Hiwi	South America	1018
Piegan	North America	1000
Batek	Asia	1

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618 Table 3: Maternal mortality ratios from four Tanzanian sources: the
619 Hadza hunter-gatherer population, the national average for Tanzania, and
620 data for two hospitals in Tanzania.

Population	MMR (per 100,000 Live Births)
Hadza	1022
Tanzanian National Average	770
Haydom Lutheran Hospital	382
Kilimanjaro Christian Medical Centre	329

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Table 4: Results of Kendall's Tau, testing the correlation between MMR and SBA, GDP per capita and presence/absence of the Neanderthal allele, and deaths due to interpersonal violence and SBA, GDP per capita and presence/absence of the Neanderthal allele.

	SBA		GDP per capita		Presence/absence of the Neanderthal allele	
	Tau	p-value	Tau	p-value	Tau	p-value
MMR	-0.6517	<0.001	-0.6433	<0.001	-0.5124	<0.001
IVMR	-0.1653	0.0018	-0.2262	<0.001	-0.0901	0.1342

Table 5: Results of partial correlation tests, determining the Tau values and p-values for each pair of variables, controlling for each other variable in turn.

Variables tested	Tau	P-value
MMR & SBA controlling for GDP	-0.4303	<0.001
MMR & SBA controlling for allele	-0.5198	<0.001
MMR & allele controlling for SBA	-0.2529	<0.001
MMR & allele controlling for GDP	-0.3195	<0.001
MMR & GDP controlling for allele	-0.5312	<0.001
MMR & GDP controlling for SBA	-0.4056	<0.001
IVMR & SBA controlling for GDP	-0.0270	0.5768
IVMR & SBA controlling for allele	-0.1376	0.0057
IVMR & allele controlling for SBA	0.0063	0.8991
IVMR & allele controlling for GDP	0.0279	0.5746
IVMR & GDP controlling for allele	-0.2135	<0.001
IVMR & GDP controlling for SBA	-0.1648	<0.001

635 Table 6: Regression coefficients and p-values for all possible models of simple and multiple
636 regression equations for MMR

	Regression coefficient							
Explanatory Variable(s)	b0	p-value	b1	p-value	b2	p-value	b3	p-value
SBA	898.25	<0.001	-859.44	<0.001				
allele	343.32	<0.001	-280.31	<0.001				
GDP	209.74	<0.001	-0.0499	<0.001				
log(GDP)	1021.59	<0.001	-102.60	<0.001				
SBA+allele	829.05	<0.001	-674.11	<0.001	-131.57	<0.001		
SBA+allele+GDP	813.50	<0.001	-648.50	<0.001	-125.30	<0.001	-93420	0.0743
SBA*allele	823.54	<0.001	-666.47	<0.001	-117.20	0.198	-17.05	0.871
SBA+log(GDP)	1071.31	<0.001	-598.82	<0.001	-46.92	<0.001		
SBA+allele+log(GDP)	970.51	<0.001	-522.00	<0.001	-104.37	<0.001	-34.47	<0.001

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639 Table 7: Adjusted R^2 values and AICc values for the regression models

Model	Adjusted R^2 value	AICc	Δ AICc	Rank
MMR~SBA+allele+GDP	0.7054	2249.415	14.461	2
MMR~SBA+allele	0.7018	2250.566	15.612	3
MMR~SBA*allele	0.7002	2252.653	17.699	4
MMR~SBA	0.6373	2285.545	50.591	6
MMR~allele	0.4283	2369.253	134.299	8
MMR~GDP	0.1771	2436.276	201.322	9
MMR~log(GDP)	0.54	2329.247	94.293	7
MMR~SBA+log(GDP)	0.6913	2256.965	22.011	5
MMR~SBA+allele+log(GDP)	0.7277	2234.954	0	1

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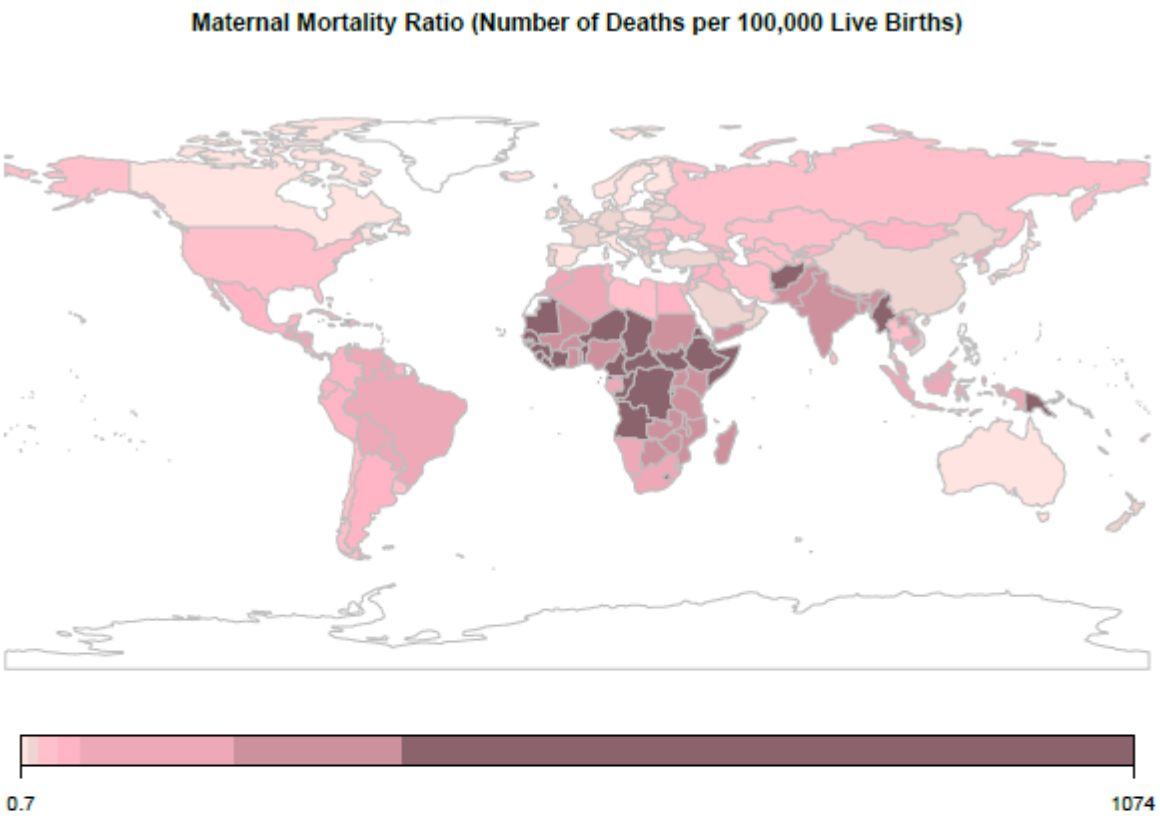
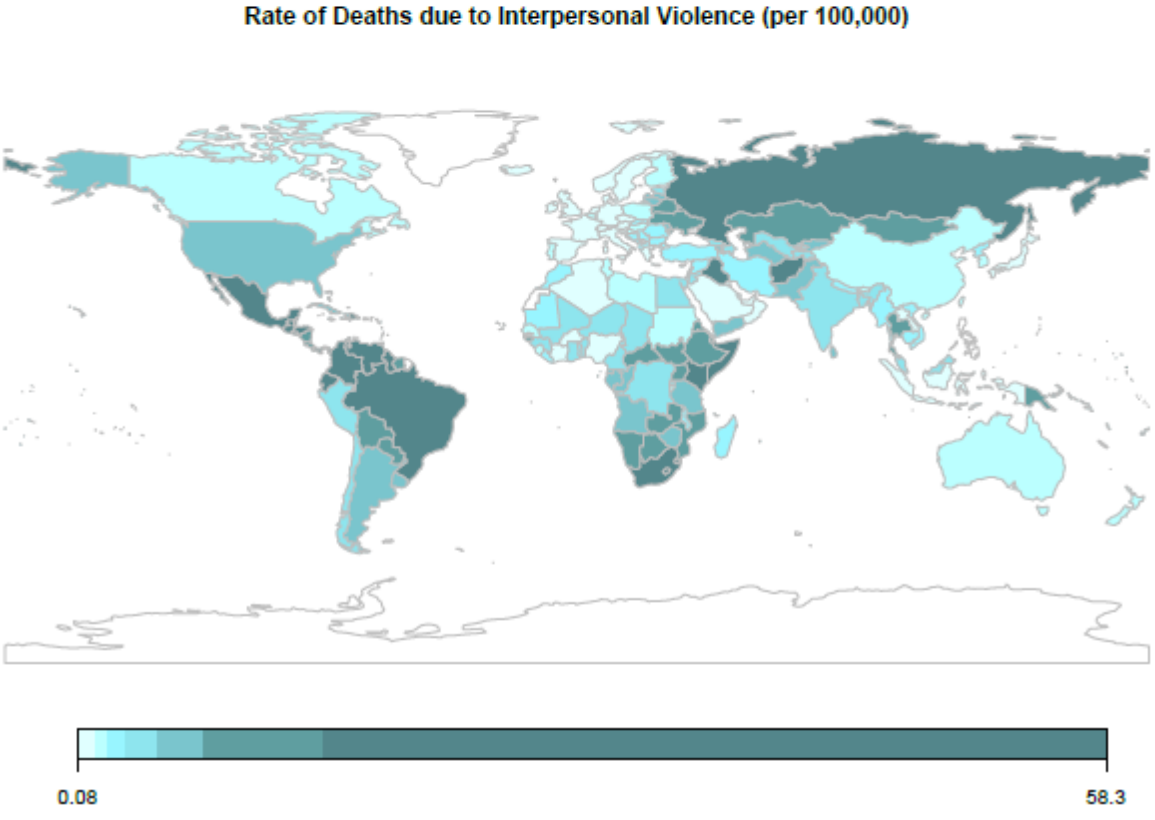
641 **Figures**

642 Figure 1





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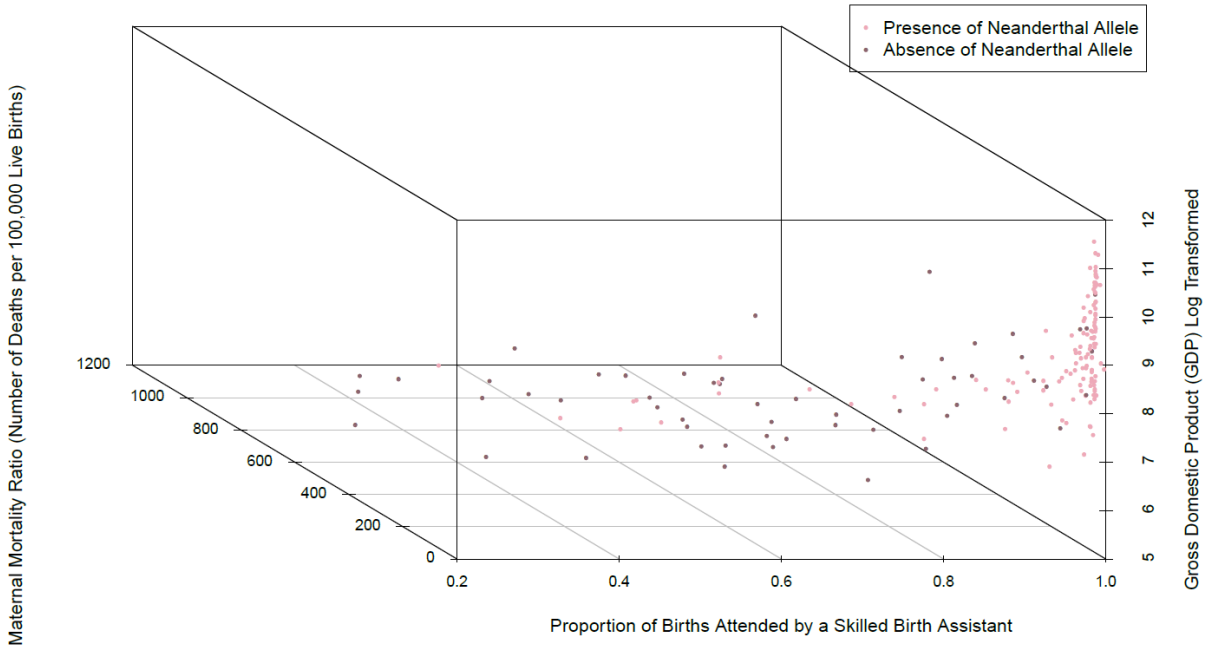
644 Figure 2



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646 Figure 3

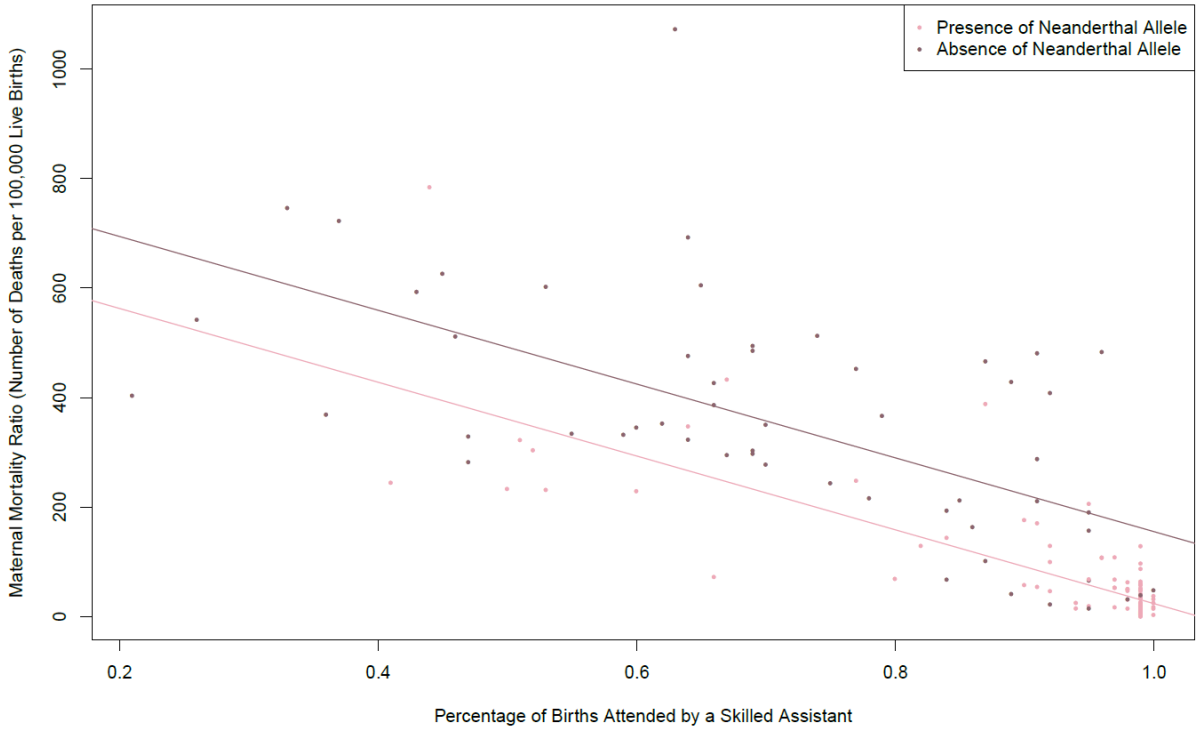

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Figure 1: World maps showing variation in maternal mortality ratios in 184 countries (top panel) and variation in deaths due to interpersonal violence for the same 184 countries (lower panel). Data is taken from the GBD 2015 SDG Collaborators (2016).

Figure 2: 3D scatter plot showing the best model for prediction of MMR variation. MMR is generally lower, and SBA generally higher for populations with the Neanderthal SNP as compared to those without, while GDP has little visible correlation with these variables.

Figure 3: Scatter plot showing the relationship between the percentage of births attended by a skilled birth assistant and maternal mortality ratios. The central tendency of populations with and without Neanderthal allele rs3917862 are shown. Countries with the Neanderthal variant are statistically significantly different in the central tendency of the distribution of MMR values.