



# ABO O gene frequency increase in the US might be causing increased maternal mortality

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## ABSTRACT

Maternal mortality rate has increased in the United States over the past 30 years from 16 deaths per 100,000 births to 28 deaths per 100,000 births while the rest of the world is experiencing declining rates. Increasing obesity and c-section rates in the US have been cited as contributing factors needing remediation, and because of the two to three fold difference in maternal mortality rates in non-Hispanic black women compared to white women, inequality and implicit racial bias has been targeted as well for remediation.

Using an epidemiologic approach, a hypothesis here brought to bear is that US immigration policy changes over the past 50 years have brought changes in the gene pool that have caused increasing obstetric hemorrhage and other causes of maternal death. ABO gene frequencies have changed in the US during this time such that ABO O, a gene associated with hemorrhage and mortality in pregnancy, has increased in frequency in the US thus increasing population maternal mortality rate.

Using mendelian randomization logic, noting the increase in ABO O gene in the US population over the past 30 years and the association of ABO O gene with both hemorrhage and lower longevity, the increase in frequency of the ABO O gene in the past 30 years in the US population might be causative of an increase in maternal mortality rate.

Consequences of this hypothesis would include recognition of the role of ABO gene and thus ABO blood group in prediction of risk of obstetric hemorrhage. Thus those at risk on this basis would be under high surveillance and would have medications and treatment strategies readily available.

While research on ABO gene and pregnancy has been done, much of the research is being done in countries other than the US, and given the increasing mortality in the US as well as the role that ABO gene may have in that, further research needs to be done in US populations to quantify risk for all adverse events in pregnancy related to ABO blood type including hemorrhage as well as inter-related causes including pre-eclampsia, cardiovascular disease, thromboembolic disease and infection.

## Introduction/background

According to the World Health Organization, maternal mortality is defined as the death of a woman whilst pregnant or within 42 days of delivery or termination of pregnancy, from any cause related to, or aggravated by pregnancy or its management, but excluding deaths from incidental or accidental causes. Late pregnancy deaths are 43 days up until 1 year. [1]

Maternal mortality rates (MMR) in the US are on the rise while those of the developing nations though still over 10–30 times that of developed nations have been on the decline over the past 30 years. This trend in decline is also seen in rates of maternal mortality of the developed world excluding the US. The increase in maternal mortality rate noted in the US from 1990 through 2015 was from 12 per 100,000 to 28 per 100,000 while developed regions of the world declined from 26 to 16. Developing regions declined from 430 to 230 during that same period. [2–6]

In reviewing subgroups of the maternal mortality rates in the US, given lower socioeconomic indicators and ethnic inequalities in non-Hispanic blacks in the US it isn't surprising that US non-Hispanic blacks have three to five times the maternal mortality rate of US non-Hispanic whites. In recent years the Center for Disease Control (CDC) reported that the mortality rate for pregnancy-related causes in the US for white women was 13 per 100,000 births, for American Indian/Alaska Native women it was 30 per 100,000 births, yet for black women it was 41 per 100,000 births. [7]

Since this happened in the face of intense efforts in quality improvement in the US [8,9] as well as advances in medical facilities and medical research both in the US as well as in the rest of the world, even taking into account world wide population changes of increasing obesity, diabetes and thus c-section rates, there is not a clear consensus on why the US MMR is increasing while that of the rest of the world is decreasing.

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## The hypothesis/theory

ABO is a genetic cause associated with hemorrhage such that ABO A would appear to associate with lower risk of hemorrhage and ABO O with a higher risk. [10–18] Because ABO blood group frequencies are different in different ethnicities [19,20], population stratification appears to be a part of the explanation for different risks of hemorrhage and maternal mortality in different world populations especially in the setting of unfavorable social determinants of health. [18–19] ABO O gene has highest frequency world wide and appears to be linked with other genetic causes of hemorrhages such as von Willebrand factor and to be associated with post partum hemorrhage and thus maternal mortality. [20]

Further, regions of the world which have high frequency of ABO A have much lower maternal mortality by a factor of three compared to the US as well as high socioeconomic indicators. So one can relate both the socioeconomic effects involving as they do such factors as universal health care and other remedies for health inequality as well as the genetic effects of differing hemorrhage risk in different regions of the world to ABO genetic variation. [18–19,21–24] So the ABO gene both as at least a marker for country of origin and as a cause of maternal mortality is relevant to causes of changes in maternal mortality. US ABO gene frequency has increased in recent years and might be a cause of increased maternal mortality in the US.

## Evaluation of the hypothesis/idea

Besides racial and ethnic inequalities and intrinsic and extrinsic bias as well as increasing US rates of obesity and diabetes, part of the increase in maternal mortality in the US may be changes in the gene pool of the US during the time of increase in maternal mortality.

Change in gene pool of a population can occur from many causes, selective pressures and migrations being common. In 1990, the population in the USA according to US Census was 248,709,873. In 2017 it was 323,148,586. This was a 30% increase predominantly from immigration pursuant to change in US immigration law in 1965 opening up to immigration from all parts of the world so that now 14% of US population is foreign born, and 50% of the population increase in US in the last 50 years is from immigration. This immigration wave was mirrored in changes in the population frequencies of ABO gene variants from ABO O 41.83%, ABO A 41.03%, ABO B 11.92%, ABO AB 5.22% prior to the immigration law changes in the US in 1965 to a higher ABO O in the present at 44%. [25–33] Among immigrants who have arrived since 1965, half (51%) are from Latin America (an area of highest prevalence of ABO O in the world) and one-quarter are from Asia (an area of very high ABO O and B and low ABO A). Indian immigrants to the US are almost overwhelmingly ABO O though the population frequencies in India are nearly equal for all ABO groups. [34] By comparison, previous immigration to the US before the civil war was of mostly southern English ancestry with high ABO A and of African ancestry with high ABO O and after the US civil war in mid nineteenth century was largely made up of European immigrants with trends toward moderate ABO O and ABO A in the case of Italian and Irish waves of immigration and higher ABO A in the case of northern European immigrants. So the trend of US population prior to 1965 reforms was of nearly equal ABO A and ABO O frequencies but of increasing ABO O frequency after 1965.

ABO gene is at chromosome 9 q34.2 [35]. ABO gene produces proteins that are found on red blood cells as well as on many other cells. [33] Variants at this genetic locus result in 4 types of cells, those carrying ABO O, those carrying ABO A, those carrying ABO B and those carrying ABO AB. These four types of cells differ in propensity to many diseases and conditions as well as inequalities in maternal mortality. [24,26–32,35–37] Besides causing such events as fetal hyperbilirubinemia, transfusion reactions and transplantation rejection, ABO gene through such mechanisms as genetic drift, selection, population

admixture and founder effect is also associated with not only many diseases and also with socioeconomic indicators.

European populations are found to have more favorable socioeconomic health indicators as well as having a population plurality of ABO A gene [18,19,21–23], the gene that it happens is less associated with hemorrhage [1,20] Populations with high maternal mortality rates and lower socioeconomic indicators have low frequency of ABO A and higher frequency of ABO O and ABO B such that ABO O is the highest frequency gene in those areas. This association of ABO gene with socioeconomic factors may add insight into the low socioeconomic status of at risk US ethnic groups having these at risk variants in the ABO gene. [35,38] The ABO gene is at least a marker for socioeconomic background of ethnic groups and their country of origin and given links with differing maternal mortality rate to regions in the world ABO gene is relevant to causes of changes in maternal mortality in the US. The ABO A association with higher national socioeconomic status shows up also in the socioeconomic inequalities noted among ethnicities in the US population that have both lower socioeconomic indicators as well as lower ABO A gene frequencies. [20,39] This gene frequency difference may be from such causes as founder effects and ancient population migration patterns.

Non-Hispanic blacks in the US have three to five times the maternal mortality compared to non-Hispanic whites and have higher ABO O gene frequency and lower ABO A gene frequency. So this hypothesis not only points to the genetic roots of the US increase in maternal mortality in recent years and the need to find predictive strategies but also adds impetus to efforts to support research to change socio-economic inequality in the US as a route to help solve the rising rate of maternal mortality. It would be expected that such strategies having been successful in decreasing maternal mortality in many countries of the developing world [40–48] would be successful here.

While it is true that hemorrhage is not the only pregnancy-related cause of maternal death, it is the cause least predictable and most rapid in its course. Causes listed with their frequencies in US maternal deaths in 2011–2014 by a CDC report in 2016 include hemorrhage (in 115%), pre-eclampsia (in 6.8%), cardiovascular disease (in 15.1%), thromboembolic disease (in 9.1%) and infection (in 12.8%). [49–64] Hemorrhage is associated with uterine atony, induction of labor, multiple gestation, grand multiparity, abnormal placenta, c section, obstetric laceration and infection. Pre-eclampsia is associated with essential hypertension, diabetes, multiple gestation, and elevations of several placental associated chemicals such as beta human chorionic gonadotropin. Infection is associated with obesity, diabetes, tearing and laceration in the birth canal, and c section. Cardiovascular disease is associated with many of the above factors as well as family history. These associations also apply to thromboembolic disease; in addition, pregnancy itself is considered a condition that independently associates with thromboembolic disease. So the causes of maternal mortality have common underlying clinical risk factors as well as heritable risk factors. But hemorrhage is the most common cause of maternal mortality worldwide. [40,41,65] Hemorrhage is the focus of this hypothesis as it occurs most rapidly and thus presents emergent need of predictive and preventive strategies.

The rate of maternal mortality is directly related to the frequency of ABO O in world wide populations. [18–19] ABO O is a gene that causes blood clotting deficits and obstetric hemorrhage. [9–16,16–17,28,66–77] Gene frequency of ABO O in the US has increased over the past 30 years directly correlating with the increase in maternal mortality. [35,46,47] While hemorrhage is not the only cause of maternal mortality, it is the cause that correlates with both changes in frequency of a gene that causes obstetric hemorrhage in the US population and with changes in maternal mortality in the US. And since hemorrhage is the most common cause worldwide, focusing on one etiology like hemorrhage allows more precise analysis of causes of changes in US maternal mortality comparing to worldwide changes in the same time period. This hypothesis if supported by more research

explains the change in maternal mortality in the US over the past 30 years and therefore leads the way to changing this dynamic.

ABO gene both codes for directly and is in linkage disequilibrium with blood clotting factors such that ABO O is associated with increased rates of rapid and thus morbid hemorrhage in pregnancy and delivery. Further, ABO gene is associated in genome wide linkage studies with mortality such that ABO O is associated with lower longevity. [38]

ABO gene's association with both mortality and with hemorrhage. [9–15,35,38,71–72] leads to the conclusion that the ABO gene is a cause of maternal mortality [16–17,37,66,72] and thus the increase in frequency of the ABO O gene that causes hemorrhage has caused the increase in US maternal mortality rate.

Further, the increase in maternal mortality in the US over the past 30–50 years correlates with the change in the US gene pool toward higher ABO O and thus higher mortality from blood clotting properties of the ABO gene. Using mendelian randomization logic, this association might be considered causative. That is, this gene produces a factor which causes deficits in blood clotting. This gene is associated with maternal hemorrhage and death so the factor produced by this gene is causing maternal hemorrhage and death.

## Consequences/discussion

Consequences of this hypothesis would include recognition of the role of ABO gene and ABO blood group testing results in prediction of risk of obstetric hemorrhage. Thus those at risk on this basis would be under high surveillance and would have medications and strategies readily available. While staff team simulations of this emergency along with blood banking efficiencies can be life saving and women in low resource settings of care are consequently at greatest risk, all women continue to be at significant risk of morbidity and mortality from hemorrhage. Even in low risk areas of the world like Europe, increased migrating and refugee patterns into Europe are beginning to be accompanied by increasing ABO O in baseline populations and increasing hemorrhage and maternal mortality. [39,40,65,71,73,74] So, besides changing factors in forced and voluntary immigration, acting on information about any pregnant patient's genetic risk of hemorrhage would further predictive and thus life-saving strategies.

There is need for more research. While much research is underway in ABO gene and pregnancy, much of the research is being done in countries other than the US, and given the increasing mortality in the US as well as the role that ABO gene may have in that, further research needs to be done in US populations to quantify risk for all adverse events in pregnancy related to ABO blood type including hemorrhage as well as entangled causes such as pre-eclampsia, cardiovascular disease, thromboembolic disease and infection.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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