Title: Geographic Latitude, Cholesterol, and Blood Pressure

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Abstract

Background In the 1980s, it was observed that people living farther from the Equator had a higher incidence of cardiovascular disease. Whether sunlight explains this finding is unknown. **Methods** We analyzed more than 180 countries' age-standardized average cholesterol, age-standardized mean systolic blood pressure, age-standardized prevalence of raised blood pressure, and death rate from ischemic heart disease, by geographic latitude. In addition to latitude, we performed analysis by ultraviolent B light exposure averaged over several years. We assessed for changes in these relationships in men and in women using data from several decades. **Results** Age-standardized mean cholesterol in men and in women increases with the distance of their country from the Equator. This relationship has changed very little since 1980. Similarly, in 1975, the mean systolic blood pressure and the prevalence of raised blood pressure were higher in countries farther from the Equator. However, the relationship between latitude and blood pressure has changed dramatically, such that by 2015, the opposite pattern was observed in women. The relationship between latitude and countries' rate of ischemic heart disease has changed in a manner tracking the changes in blood pressure. Countries' average ultraviolet B light exposure has a stable relationship with cholesterol over recent decades, but has a changing relationship with blood pressure. **Conclusions** Since sunlight exposure in a country averaged over several years is relatively fixed and since its relationship with blood pressure has changed dramatically in recent decades, countries' average sunlight exposure is an unlikely explanation for contemporary country-level variation in blood pressure. However, our findings are consistent with a putative effect of sunlight on countries' average cholesterol, as well as a no longer detectable effect on blood pressure decades ago. A parsimonious potential explanation for the relationship between light and cholesterol is that 7-dehydrocholesterol can be converted to cholesterol, or in the presence of ultraviolet light, it can instead be converted to vitamin D. Nonetheless, other explanations can be hypothesized.

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Introduction

In the 1980s, the incidence of cardiovascular disease was noted to be higher in countries farther from the Equator.[1] A popular hypothesis is that sunlight exerts a protective effect by reducing cholesterol and/or blood pressure.[2-4] A classic study in rabbits[5] and a more recent study in mice,[6] a cross-sectional study of humans,[7] and a small clinical trial[4] provide evidence of an effect of ultraviolet radiation on cholesterol. A parsimonious potential explanation is that 7-dehydrocholesterol can be converted to cholesterol, or in the presence of ultraviolet light, it can instead be converted to vitamin D.[4,6] Sunlight's effect on blood pressure is hypothesized to have a more complex biological basis, which might involve vitamin D, nitric oxide, and melanin.[8] There is experimental evidence to support an effect of ultraviolet B light on blood pressure.[9] Whether effects of sunlight on cholesterol or blood pressure manifest at the level of global health is not well understood since most ecological studies relating sunlight exposure and/or latitude to cardiovascular risk factors are old and cross-sectional and involve relatively few countries.

New treatments for elevated cholesterol and blood pressure have been developed and disseminated since the 1970s, even as changes in health habits have swept the globe. It is possible that the relationship between latitude and cholesterol or blood pressure has changed accordingly, suggesting that sunlight is at most a small factor compared to other aspects of lifestyle. If instead, latitude or ultraviolet radiation has an unchanged relationship with a cardiovascular risk factor over decades despite lifestyle changes, a role for sunlight is more likely. Using decades of longitudinal data from over 180 countries, we examined the relationship between latitude and total cholesterol, systolic blood pressure, and death from ischemic heart disease, with attention to changes over time. We also examined the relationship between ultraviolet B light exposure and countries' cholesterol or blood pressure. In addition, we examined whether sex differences exist in these relationships.

Methods

We obtained the country latitudes used in Google's Public Data Explorer project.[10] From the World Health Organization's (WHO) Global Health Observatory,[11] we obtained country-level age-standardized estimates of: mean total cholesterol (1980-2009), mean systolic blood pressure (1975-2015), and the prevalence of raised blood pressure (1975-2015). Raised blood pressure was defined by WHO as systolic blood pressure≥140 mm Hg or diastolic blood pressure≥90 mm Hg). Additional methods underlying the blood pressure measurements have been published.[12]

We obtained countries' 1995-2015 ischemic heart disease mortality rate from the Global Burden of Disease study via the Global Data Health Exchange database.[13] In addition, we obtained country-level ultraviolet B light exposure (averaged between 1997-2003) from the WHO Global Health Observatory. We used local regression (LOESS) plots to visualize the relationship between latitude and these endpoints. We also calculated Spearman correlation coefficients for distance from the Equator and countries' mean cholesterol, mean systolic blood pressure, or the prevalence of raised blood pressure. We further evaluated whether our findings were stable over recent decades. Analyses were performed using R 3.4.3.[14]

Results

Latitude-based analyses included 188 countries' mean cholesterol values, 180 countries' mean systolic blood pressures, 189 countries' prevalences of raised blood pressure, and 189 countries' coronary heart disease mortality rates. Ultraviolet B radiation exposure-based analyses included 185 countries' mean cholesterol values and 186 countries' raised blood pressure prevalences.

Since at least the 1980s, average total cholesterol has been lowest in women (**Figure 1A**) and men (**Figure 1B**) living in countries at or near the Equator and has increased symmetrically with distance north or south of the Equator. Despite a downward shift in countries' average cholesterol over recent decades, this symmetry around the Equator has been preserved. Absolute distance of a country from the Equator has correlated with total cholesterol in women (**Figure 1C**) and men (**Figure 1D**) since at least the 1980s ($r_s = 0.66$, $P<2.2e^{-16}$ [females]; $r_s = 0.67$, $P<2.2e^{-16}$ [males] in 1980; $r_s = 0.51$ $P=1.2e^{-13}$ [females]; $r_s = 0.57$, $P<2.2e^{-16}$ [males] in 2009).

In 1975, countries' mean systolic blood pressure followed a pattern similar to mean cholesterol, with systolic blood pressure increasing with distance north or south of the Equator in females (**Figure 2A**) and to a lesser extent in males (**Figure 2B**). As with cholesterol, countries' mean systolic blood pressure exhibited symmetry north and south of the Equator. In contrast to cholesterol, mean systolic blood pressure's relationship with latitude has been unstable over time. In fact, by 2015, the pattern had reversed itself in females (**Figure 2A**). In males, countries' mean systolic blood pressure had a complex, bimodal relationship with latitude in 2015 (**Figure 2B**). Particularly in females, the changes in latitude's relationship with age-standardized mean systolic blood pressure have been similar in the Northern and Southern hemispheres, preserving the north-south symmetry seen in the 1970s, with the Equator appearing as an inflection point. The slope of the relationship between absolute distance from the Equator and mean systolic blood pressure has been decreasing over time in females (**Figure 2C**)--in whom it has reversed direction in recent years to a negative relationship--and in males (**Figure 2D**, $r_s = 0.52$, $P=4.0e^{-14}$ [females]; $r_s = 0.49$, $P=2.9e^{-12}$ [males] in 1975; $r_s = -0.28$, $P=0.0002$ [females]; $r_s = 0.07$, $P=0.32$ [males] in 2015). Compared to mean systolic blood pressure, countries' prevalences of raised blood pressure had similar LOESS plots (**Figures 3A and 3B**), but stronger symmetry around the Equator and marginally stronger correlation in in the 1970s ($r_s = 0.57$, $P<2.2e^{-16}$ [females]; $r_s = 0.60$, $P<2.2e^{-16}$ [males] in 1975; $r_s = -0.29$, $P=4.9e^{-5}$ [females], $r_s = 0.13$, $P=0.09$ [males] in 2015, **Figure 3**).

The relationship between ultraviolet B radiation and cholesterol or blood pressure mirrored their relationships with latitude. For decades, countries with higher average ultraviolet B radiation levels have had lower mean cholesterol in females (**Figure 4A**) and males (**Figure 4B**). As with latitude, the relationship between ultraviolet B radiation and raised blood pressure has been changing over time, with clear reversal of this relationship in females in 2015 compared to 1975 (**Figure 4C**) and dramatic changes in males (**Figure 4D**). The relationship between countries' ultraviolet B radiation exposure and death from ischemic heart disease per 100,000 people has been changing since at least 1990 in females (**Figure 5A**) and males (**Figure 5B**).

Discussion

The major new findings of this study are that for at least four decades, males' and females' average cholesterol levels have been higher in countries farther from the Equator, whereas mean systolic blood pressure and the prevalences of raised blood pressure showed a similar pattern decades ago, but no longer. In women, blood pressure's relationship with latitude has reversed over time. Countries' average ultraviolet B radiation has had a relatively constant relationship for decades with their populations' mean cholesterol. The relationship between countries' average ultraviolet B radiation exposure and blood pressure has changed dramatically over time, and the latitude-ischemic heart disease death rate relationship has closely tracked these changes.

In a small study (n=338) conducted at three sites in British Columbia, plasma cholesterol decreased with increasing latitude, a finding the authors attributed to differences in Rhesus Blood Group system.[15] Conversely, hypertension prevalence or blood pressure have been reported to increase with distance north or south of the Equator or with increased solar radiation exposure within single countries[16,17] and in studies of smaller groups of countries[3,18] than we have analyzed. However, adjusting for vitamin D levels had no effect on the solar radiation-blood pressure relationship in a recent study, suggesting blood pressure's variation by solar radiation levels is not mediated by vitamin D.[17] Public availability of high-quality data facilitated our more comprehensive analysis of latitude's and ultraviolet B radiation's relationship with males' and females' cardiovascular risk factors estimated at the national level, around the globe and over decades. Our findings contrast with the prior single-country analysis of latitude and cholesterol, suggesting a possible Simpson's paradox, in which findings at a smaller scale of analysis are at odds with findings at a larger scale of analysis. Our latitude-blood pressure findings using data from decades ago are consistent with results from decades ago, but since then, the relationship not only has changed in men, it has reversed in women.

The factors explaining the stable relationship between countries' latitude and their populations' cholesterol are likely different from those explaining the relationship between latitude and blood pressure, which has changed dramatically over time. Exposure to sunlight has been proposed to explain the relationship between latitude and blood pressure,[8] but the marked changes in the relationship indicate it is no longer a key determinant of country-level differences in blood pressure, if it once was. Increased sunlight lowers cholesterol in experimental settings in rabbits and humans.[4,5] Sunlight exposure could plausibly explain or contribute to the more stable relationship between latitude and cholesterol. An indirect effect of sunlight on cardiovascular risk factors through differences in agriculture is an alternate, plausible explanation of the relationship between UV light and cholesterol. There are likely other plausible explanations, as well.

Strengths of the current study include longitudinal analysis of high-quality data from more than 180 countries and the bringing together of multiple publicly available datasets to throw new light on an old question. The principal limitation of the study is its ecological nature, since ecological studies can show us what is true around the globe, but they permit only relatively weak inferences about how to explain what is seen. A second limitation is that our analysis compared countries' UV B light exposure averaged between 1997-2003 to risk factors collected over a broader time span. Our analysis assumes stability of UV B light exposure, whereas there have been some regional changes in UV B light exposure due to the hole in the ozone layer. This issue affects only the UV B light analyses.

Ischemic heart disease (IHD) is the leading cause of death globally. A long-term 10% reduction in total cholesterol lowers risk of ischemic heart disease by 50% at age 40 and 20% at age 70,[19] and a 20 mm Hg lower usual systolic blood pressure is associated with a 50% decrease in death from IHD and 50% decrease in death from stroke.[20] As we seek new means of understanding cardiovascular risk reduction, additional studies to better understand the effect of sunlight on cardiovascular risk are needed.

Declaration of Interests

The authors have no conflicts of interest.

Acknowledgements

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Figure Legends.

Figure 1. LOESS plots of latitude and countries' mean total cholesterol (age-standardized) in females (**Panel A**) and males (**Panel B**). The vertical dotted lines represent 23.5 degrees North and South, the Tropics of Cancer and Capricorn, which define the tropics. LOESS plots of absolute distance from the Equator in degrees and countries' mean total cholesterol (age-standardized) in females (**Panel C**) and males (**Panel D**).

Figure 2. LOESS plots of latitude and countries' mean systolic blood pressure (age-standardized estimate) in females (**Panel A**) and males (**Panel B**), using data from every 10 years between 1975 and 2015. **Panels C** and **D** are LOESS plots of absolute distance from the Equator in degrees and countries' mean systolic blood pressure (age-standardized estimate) in females and males, respectively.

Figure 3. LOESS plots of latitude and countries' prevalence of raised blood pressure (SBP≥140 or DBP≥90 [age-standardized estimate]) in females (**Panel A**) and males (**Panel B**), using data from every 10 years between 1975 and 2015. The vertical dotted lines represent 23.5 degrees North and South, the Tropics of Cancer and Capricorn, which define the tropics. **Panels C** and **D** are LOESS plots of absolute distance from the Equator in degrees and countries' prevalence of raised blood pressure in females and males, respectively.

Figure 4.

LOSS plots of countries' distance from the Equator and their populations' rate of death from ischemic heart disease per 100,000 population in females (**Panel A**) and males (**Panel B**).

Figure 5.

LOESS plots of countries' log-transformed ultraviolet B radiation exposure (averaged between 1997-2003) and their populations' mean cholesterol in females (**Panel A**) and males (**Panel B**). LOESS plots of the relationship between log-transformed ultraviolet B radiation exposure and prevalence of raised blood pressure (SBP≥140 or DBP≥90 [age-standardized estimate]) in females (**Panel C**) and males (**Panel D**).

Figure 1.

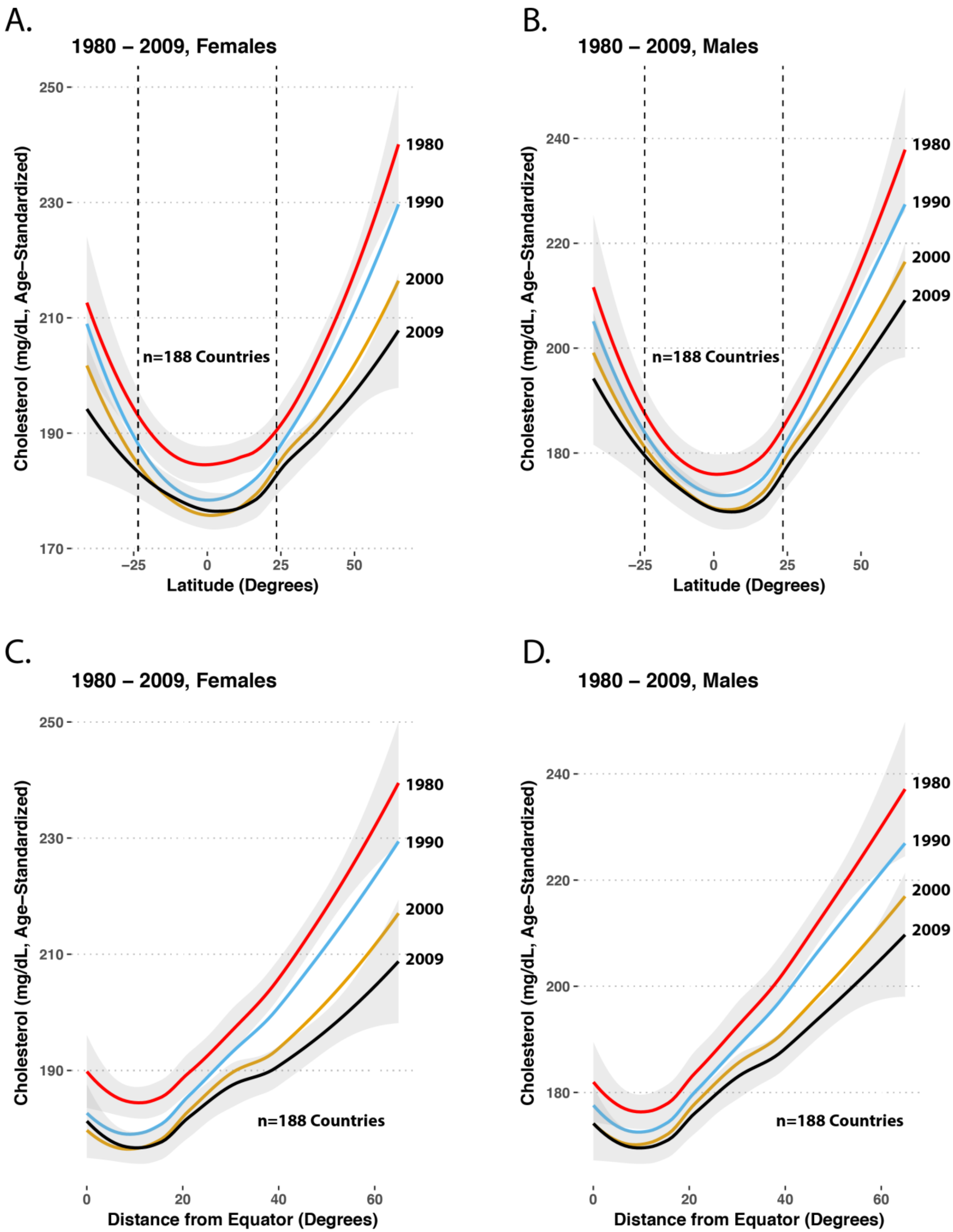

A.
1980 – 2009, Females
Cholesterol (mg/dL, Age–Standardized)
Latitude (Degrees)
n=188 Countries
1980
1990
2000
2009
B.
1980 – 2009, Males
Cholesterol (mg/dL, Age–Standardized)
Latitude (Degrees)
n=188 Countries
1980
1990
2000
2009
C.
1980 – 2009, Females
Cholesterol (mg/dL, Age–Standardized)
Distance from Equator (Degrees)
n=188 Countries
1980
1990
2000
2009
D.
1980 – 2009, Males
Cholesterol (mg/dL, Age–Standardized)
Distance from Equator (Degrees)
n=188 Countries
1980
1990
2000
2009

Figure 2.

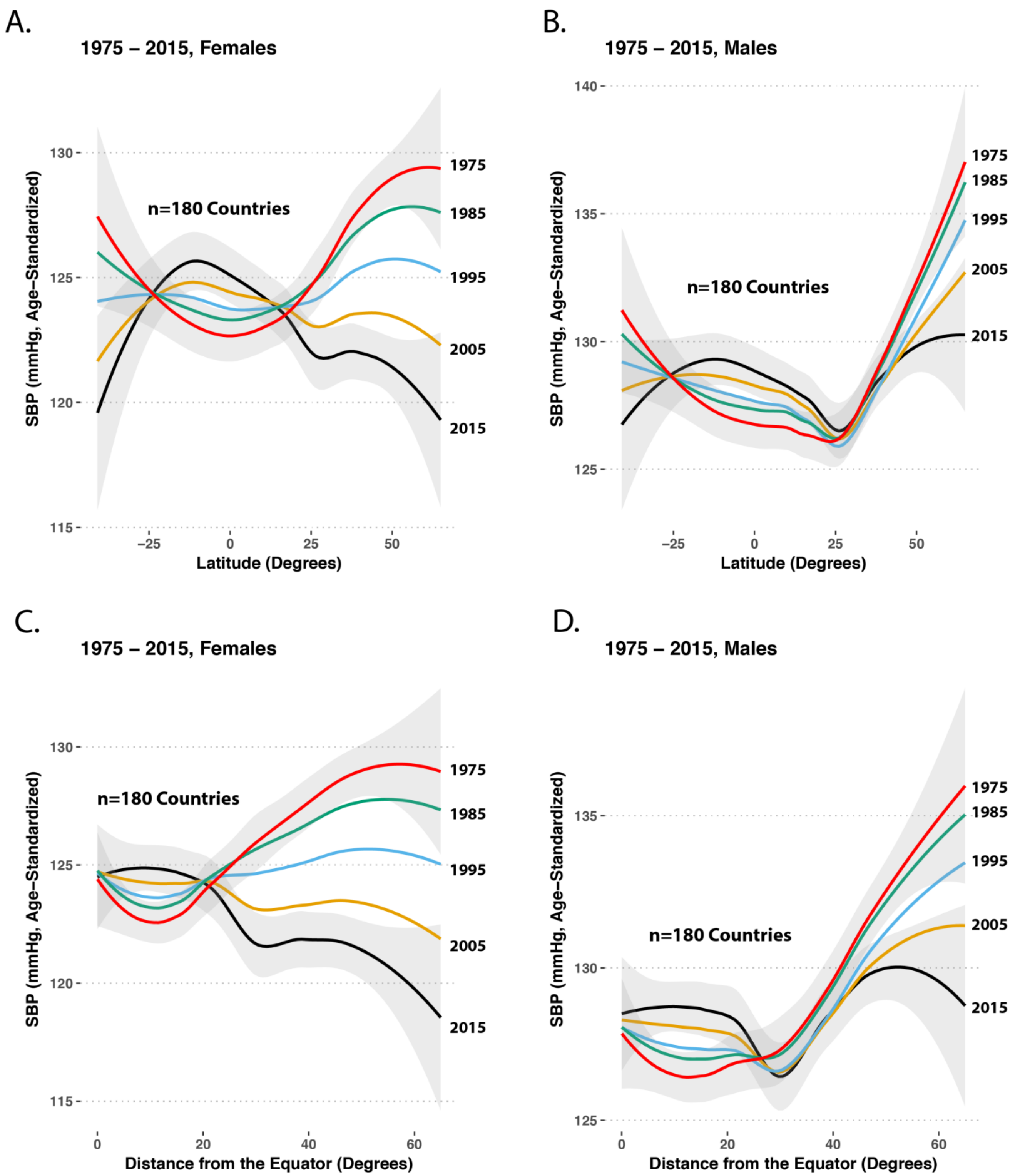

A.
1975 – 2015, Females
n=180 Countries
SBP (mmHg, Age–Standardized)
Latitude (Degrees)
1975
1985
1995
2005
2015
B.
1975 – 2015, Males
n=180 Countries
SBP (mmHg, Age–Standardized)
Latitude (Degrees)
1975
1985
1995
2005
2015
C.
1975 – 2015, Females
n=180 Countries
SBP (mmHg, Age–Standardized)
Distance from the Equator (Degrees)
1975
1985
1995
2005
2015
D.
1975 – 2015, Males
n=180 Countries
SBP (mmHg, Age–Standardized)
Distance from the Equator (Degrees)
1975
1985
1995
2005
2015

Figure 3.

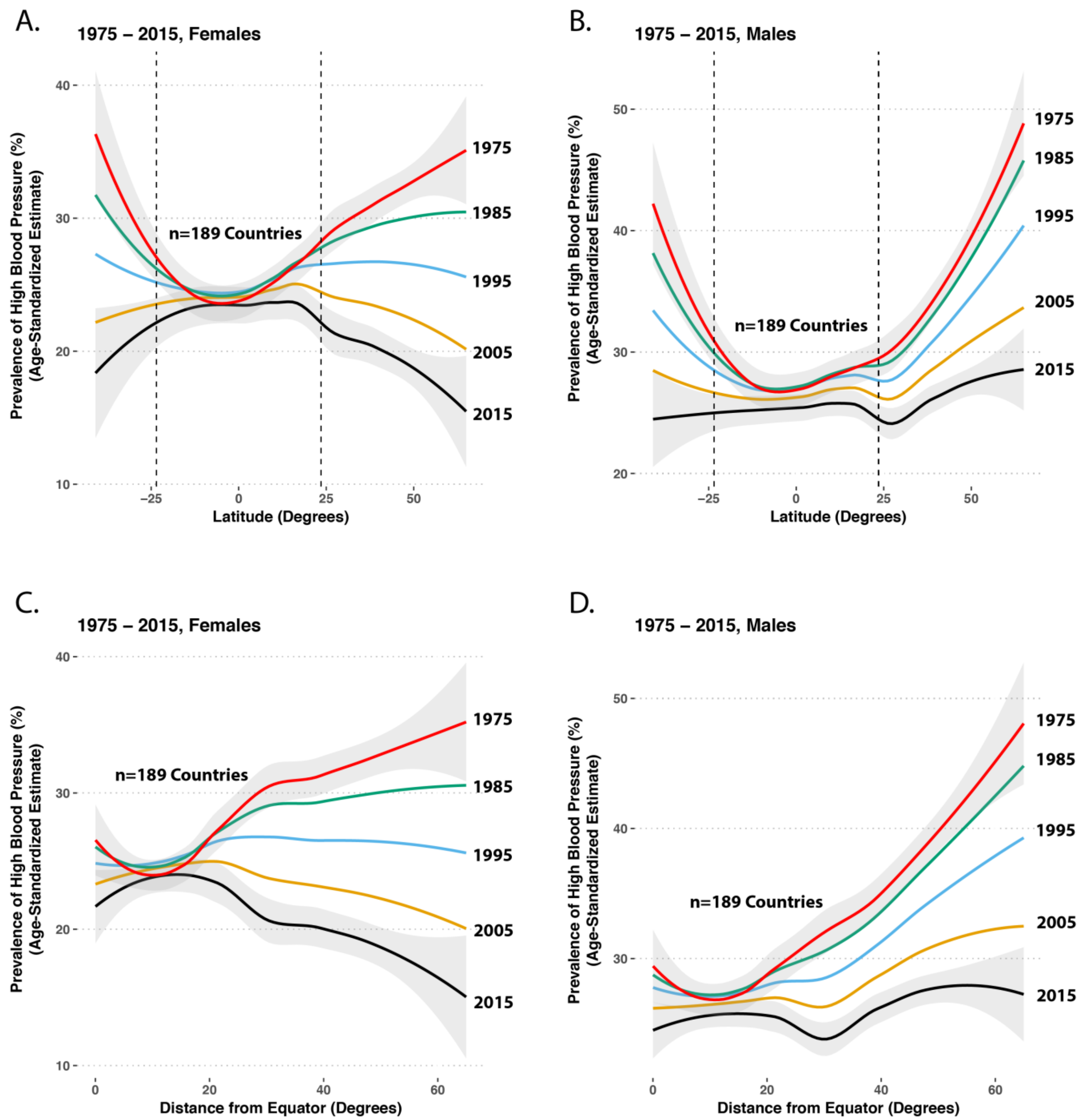

A.
1975 – 2015, Females
n=189 Countries
1975
1985
1995
2005
2015
Prevalence of High Blood Pressure (%) (Age-Standardized Estimate)
Latitude (Degrees)
B.
1975 – 2015, Males
n=189 Countries
1975
1985
1995
2005
2015
Prevalence of High Blood Pressure (%) (Age-Standardized Estimate)
Latitude (Degrees)
C.
1975 – 2015, Females
n=189 Countries
1975
1985
1995
2005
2015
Prevalence of High Blood Pressure (%) (Age-Standardized Estimate)
Distance from Equator (Degrees)
D.
1975 – 2015, Males
n=189 Countries
1975
1985
1995
2005
2015
Prevalence of High Blood Pressure (%) (Age-Standardized Estimate)
Distance from Equator (Degrees)

Figure 4.

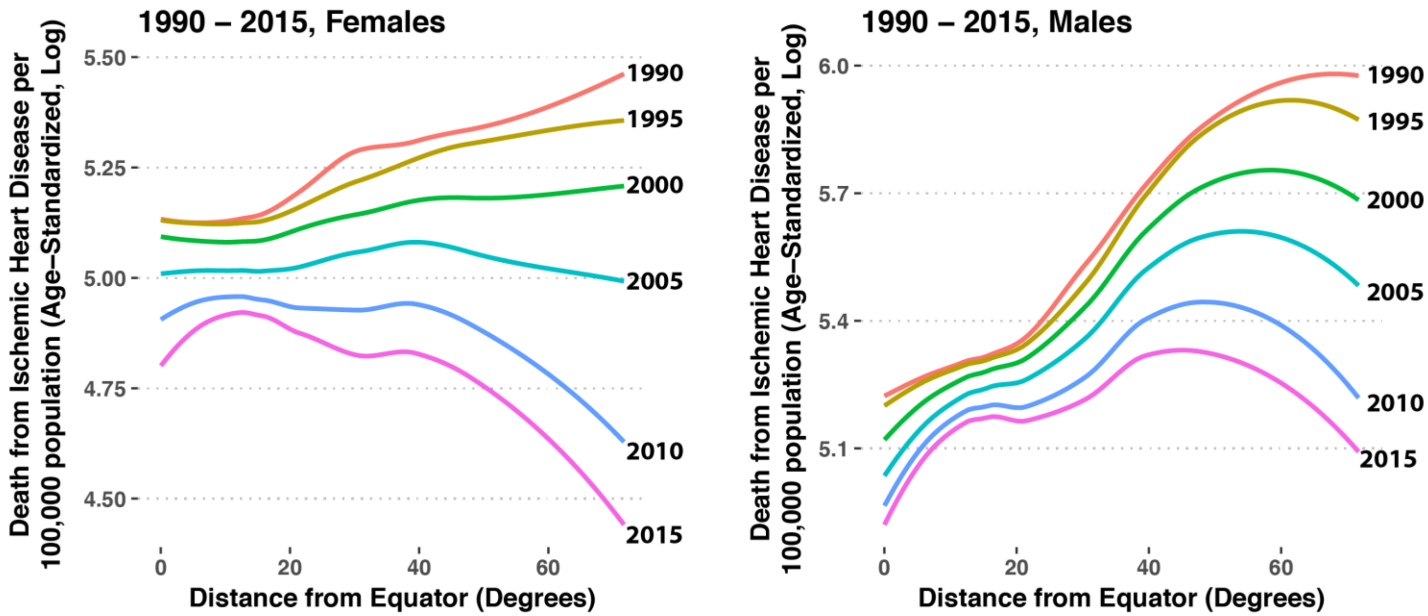
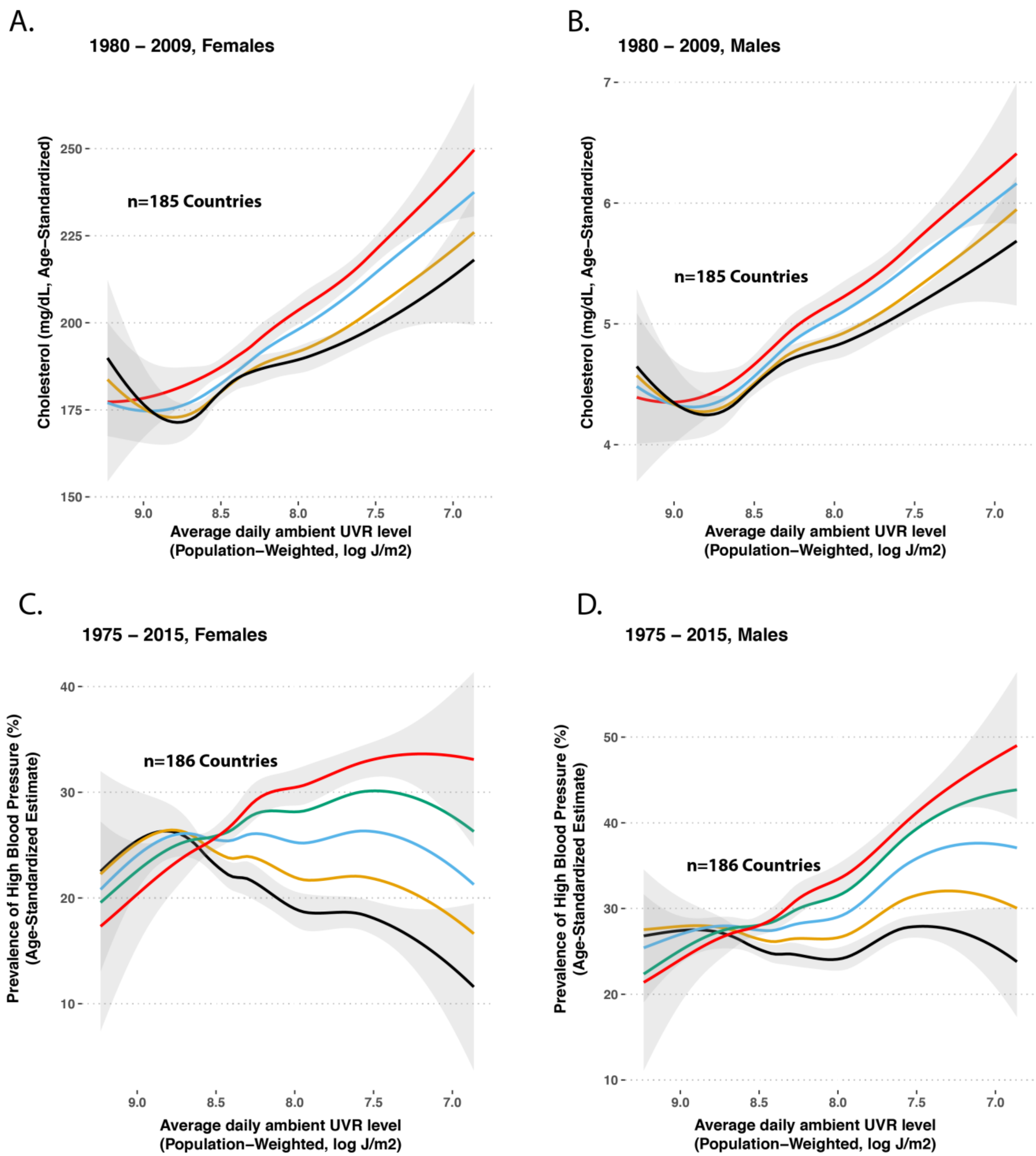

1990 – 2015, Females
Death from Ischemic Heart Disease per 100,000 population (Age-Standardized, Log)
5.50
5.25
5.00
4.75
4.50
0
20
40
60
Distance from Equator (Degrees)
1990
1995
2000
2005
2010
2015
1990 – 2015, Males
Death from Ischemic Heart Disease per 100,000 population (Age-Standardized, Log)
6.0
5.7
5.4
5.1
0
20
40
60
Distance from Equator (Degrees)
1990
1995
2000
2005
2010
2015

Figure 5.


A.
1980 – 2009, Females
n=185 Countries
Cholesterol (mg/dL, Age−Standardized)
250
225
200
175
150
9.0
8.5
8.0
7.5
7.0
Average daily ambient UVR level
(Population−Weighted, log J/m2)
B.
1980 – 2009, Males
n=185 Countries
Cholesterol (mg/dL, Age−Standardized)
7
6
5
4
9.0
8.5
8.0
7.5
7.0
Average daily ambient UVR level
(Population−Weighted, log J/m2)
C.
1975 – 2015, Females
n=186 Countries
Prevalence of High Blood Pressure (%)
(Age-Standardized Estimate)
40
30
20
10
9.0
8.5
8.0
7.5
7.0
Average daily ambient UVR level
(Population−Weighted, log J/m2)
D.
1975 – 2015, Males
n=186 Countries
Prevalence of High Blood Pressure (%)
(Age-Standardized Estimate)
50
40
30
20
10
9.0
8.5
8.0
7.5
7.0
Average daily ambient UVR level
(Population−Weighted, log J/m2)

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