Cognitive epidemiology of ethnic health and the CHRM2 vagal vigour hypothesis

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Ethnic populations representing areas throughout California were compared regarding cognitive ability, socioeconomic position, and mortality. Cognition and socioeconomic position were inversely correlated with mortality. The single nucleotide polymorphism rs8191992 in the M2 muscarinic receptor gene (CHRM2) was previously linked to IQ and modulation of vagal tone. The CHRM2 vagal vigour hypothesis posits that variation at rs8191992 alters the binding site for a brain-expressed microRNA (hsa-mir-383) thereby changing expression of brain M2 muscarinic receptors to cause pleiotropic effects on cognition and vagus nerve signalling which then affects health via the vagal cholinergic anti-inflammatory pathway. This may help explain ethnic health differences, including the Hispanic Health Paradox, since ethnic differences in rs8191992 allele frequencies correspond to ethnic differences in systemic inflammation and mortality. The rs8191992 A-allele may contribute to the clustering of low IQ and low vagal tone with higher substance abuse, externalizing psychopathology, depression, systemic inflammation, metabolic syndrome, and cardiovascular disease.

The associations of socioeconomic position (SEP) and ethnicity with differences in health and mortality have long been a focus of research in sociology and epidemiology[1, 2]. In addition to being linked to health and mortality, SEP and ethnicity show substantial associations with IQ[3-5]. With the advent of cognitive epidemiology, growing attention has been directed toward studies of the links between IQ and health[6-9]. An essay introducing the new field of cognitive epidemiology listed four items as high IQ-associated factors that might serve as links to better health[9]:

1) Higher education and SEP leading to healthier home and work environments.

2) Healthier behaviours such as diet, exercise and smoking habits.

3) Fewer injuries and illnesses sustained during youth.

4) A more well-wired body with higher system integrity.

The fourth item, with its connotation of innate biological differences in disease susceptibility, is somewhat akin to the genetic hypothesis presented here, i.e. that a gene might exert pleiotropic effects on both cognition and health-related physiology.

IQ is strongly correlated with academic achievement test performance and IQ is moderately correlated with SEP measures such as educational attainment, occupational status, and income[3, 10, 11], thus it is often difficult to disentangle IQ-effects from SEP-effects. Therefore a gene allele that modulates IQ might also tend to correlate with SEP, and if the same gene allele also exerts pleiotropic effects on a physiological pathway that affects disease susceptibility, then the resulting phenotype could manifest as covariation in IQ, SEP, and health. A study of the mortality of all persons who were born in Denmark from 1924-1947 and who were adopted at young ages, found that the adoptees' adult mortality rates correlated inversely with the SEPs of their biological fathers but no correlation was seen with the SEPs of their adoptive fathers[12]. These

results suggest the genetic transmission of some factor (e.g. a gene allele that modulates both IQ and health) that correlates with higher parental SEP and that is also linked to lower mortality in the biological offspring. This in fact is the essence of the hypothesis presented here, the CHRM2 vagal vigour hypothesis, which posits a genetic linkage between ethnicity, IQ, SEP and health. This hypothesis will probably prove controversial because of the Nature-Nurture controversy. The Nature-Nurture debate involves a conflict between two schools of thought regarding the causes of ethnic and social class variations in mental traits (Supplementary Table 1). The Galtonians (Hereditarians) see ethnic genetic differences as a major determinative factor, while the Boasians (Environmentalists) reject the involvement of ethnic genetic differences and instead see the persistence of ethnic disparities in political and economic power and deep cultural differences as the salient issues. Galtonians tend to see gene-based IQ differences as a proximate cause for differences in educational achievement, SEP, and culture. Boasians tend to see IQ differences as a consequence of pre-existing differences in culture, educational achievement, and SEP. The CHRM2 vagal vigour hypothesis reflects the Galtonian perspective but it is hoped that this hypothesis will provoke critical discussion and stimulate further research toward understanding the nature of associations between ethnicity, IQ, SEP, and health.

Standardized mathematics achievement test scores as an index of cognitive ability
Academic achievement test scores, particularly mathematics scores, are highly correlated with general cognitive ability and the correlation is largely genetic[3, 10, 11]; thus these widely available test scores can serve as a useful resource for gauging population IQ levels[13]. In the USA, as a result of the 2001 No Child Left Behind federal education

initiative, most states have administered academic achievement tests ("Standards

Tests") to nearly all public school students. The 7th Grade (~13 year old students)

California Standards Test (CST) mathematics scores from throughout California were

collated and converted to standard score format (the IQ-metric with 15 points = 1 SD)

with 100 representing the average of the statewide White population. The statewide

CST Mathematics scores (Supplementary Fig. 1) show substantial differences in the

average IQs of the various ethnic populations ranging from African Americans at ~85 to

East Asians (Japanese, Koreans, and Chinese) at ~111. For further analyses, the

cognitive ability scores of the various Asian subgroups (including Filipinos but not

Pacific Islanders) were aggregated to produce a total Asian group that corresponds with

the available census and mortality data. The scores from each of four years (2003-2006)

were averaged to estimate the mean IQs of the various ethnic populations

(Supplementary Fig. 2); and the resulting group IQ scores (Black 85.2, Hispanic 87.7,

American Indian 90.6, White 100.0, and Asian 104.6) were found to be similar to

previously reported values[4, 5].

Cognitive epidemiology of ethnicity, SEP, and mortality in California

Using a geographic area-based measures approach, the state of California was divided

into 220 area zones corresponding to low population counties, individual school

districts, the seven learning districts which comprise the Los Angeles school district,

and aggregates of adjoining smaller school districts. Using CST 7th Grade 2003-2006

Mathematics scores, average IQ estimates were determined for the populations residing

within each zone and plotted against an index of SEP that reflects the prevalence of

college graduates and high household incomes within the total population of each zone

(Fig. 1a) or within the ethnic populations of each zone (Fig 1d). These data show that variations in the level of cognitive ability between different area populations correlate strongly (r = .86) with variations in their SEP. There is a strong inverse correlation between the SEPs of the various regional populations and their mortality at ages 55 to 64 (Fig. 1b). In the USA the mortality of Hispanics is lower than expected in view of their low SEP, this is known as the Hispanic Health Paradox[14]. When the data are disaggregated into ethnic groups the Hispanic populations show lower mortality than some White populations of higher SEP (Fig. 1e), thus these data exhibit the classic Hispanic Health Paradox (low mortality associated with low SEP). Cognitive ability also shows a strong inverse correlation with mortality in the total population data (Fig. 1c). With the ethnic population data, a new manifestation (low mortality associated with low IQ) of the Hispanic Health Paradox is evident in which Hispanic populations tend to show lower mortality than some White populations of higher average cognitive ability (Fig. 1f). In the USA, persons of full or partial Native American ancestry are usually designated as "American Indians" if their ancestors lived north of the USA-Mexico border but they are usually designated as "Hispanics" if their ancestors lived south of the border; thus genetic similarity between Hispanics and Native Americans is expected and has been documented[15]. The current data show similarity between Hispanics and American Indians in regard to IQ, SEP and mortality suggesting that a phenomenon similar to the Hispanic Health Paradox also involves the American Indian population.

To investigate with more power the pattern of the relationships between IQ, ethnicity, and mortality, area populations of similar average IQ and of the same ethnicity from different zones from throughout the state were collated and aggregated

into larger groups. The Asian, Hispanic and Black populations were each binned into tertile groups, while the much larger White population was binned into hexile groups, and the less numerous American Indian population was collated into one group. For clarification, the relationship between ethnicity and IQ and total natural cause mortality (at ages 55 to 64) is displayed in both unbinned (Fig. 1f) and binned (Fig. 1g) formats. Also shown are ethnicity and IQ in relation to mortality due to cardiovascular diseases (Fig. 1h) and cancers (Fig. 1i). To assess the validity of these IQ versus mortality plots of ethnic population data from California, a similar analysis was performed on nation-wide ethnic population cognitive test score (2000, 2003, 2005, & 2007 NAEP National 8th Grade Mathematics) and mortality (1997-2005 Center for Disease Control National Vital Statistics System) data; the nationwide ethnic group data points (larger unfilled symbols) align moderately well with the midrange points from the California ethnic populations (Fig. 1g,h,i); thus confirming the validity of these analyses. The proportions of mortality which are due to various specific diseases and external causes are illustrated for the collated IQ/ethnic populations for both men and women (Supplementary Figures 3 & 4); these data suggest that the association between IQ and mortality and the Hispanic Health Paradox effect is rather similar in both sexes. The relationship of ethnicity and IQ to mortality at various ages due to external causes (chiefly accidents, homicide and suicide) is shown (Supplementary Fig. 5). Suicides are seen to be particularly prevalent in lower IQ Whites and homicide deaths are extremely prevalent in younger lower IQ Blacks. The relationships of ethnicity and IQ to mortality at various ages due to non-cancer natural causes (Supplementary Fig. 6) and cancers (Supplementary Fig. 7) are also shown. The inverse relationship between IQ and mortality is seen to be most evident in cardiovascular disease, chronic lung disease

(asthma/COPD/emphysema), and in some cancers involving the aerodigestive tract (head and neck, lung, oesophagus, pancreas, and colon) and the urinary tract (kidneys and bladder). No obvious IQ effect is evident in rates of deaths due to melanoma or sarcoma or from tumours of the stomach, biliary tract, breast, ovaries, uterus, prostate, or brain.

The CHRM2 vagal vigour hypothesis

The concept of a mind-body connection mediated by the vagus nerve has been studied since the time of Claude Bernard but in the past decade there has been growing interest in the vagal mind-body connection with Tracey's discovery of the vagal cholinergic anti-inflammatory pathway[16] and Thayer's development of the neurovisceral integration model which focuses on interconnections between emotive and cognitive brain functions, vagal tone (frequency of vagal signalling), and psychological and physical health[17]. Vagal tone is usually measured by one of three methods: heart rate variability (HRV), heart rate recovery (HRR), or respiratory sinus arrhythmia (RSA). The CHRM2 vagal vigour hypothesis (Fig. 2) incorporates prior concepts such as the vagal cholinergic anti-inflammatory pathway[16] and some aspects of the neurovisceral integration model[17], but importantly this new hypothesis includes a specific molecular genetic connection between cognition and vagal tone by postulating that the derived T-allele of the CHRM2 3-prime untranslated region (3'UTR) single nucleotide polymorphism (SNP) rs8191992 exerts pleiotropic effects to increase both cognitive functioning (which then indirectly results in increased SEP) and vagal nerve signalling (which results in better health via the cholinergic anti-inflammatory pathway). This

CHRM2 vagal vigour hypothesis also raises the suggestion that ethnic variation in rs8191992 allele frequency is a cause for ethnic variation in health and mortality. Three research groups have reported that variations in CHRM2 SNPs are linked to variation in IQ, in particular the T-alleles of SNPs rs324650 and rs8191992 have been associated with increased IQ[18-20] (information about these three studies, and about one negative study, is presented in Supplementary Table 2). The T-allele of rs8191992 has also been associated with increased vagal tone[21, 22]. In regard to six SNPs (rs324650, rs8191992, rs6962027, rs6967953, rs1378650, rs17506824) located in the 3-prime region of the CHRM2 gene (Fig. 2a), in Asians the most common linkage haplotype is TTTTTT, in Blacks AAACCC is common, whereas Whites have a mixture of haplotypes (Fig. 2b and Supplementary Fig 8). Based on the available data, it appears that Native Americans resemble Asians in their allele frequencies within this genomic region and that Hispanics are intermediate between Whites and Asians (Fig. 2b).

In addition to IQ[18-20] and vagal tone[21, 22], SNP variations in the CHRM2 gene have been associated with depression, and disinhibitory psychological disorders including alcoholism, drug abuse, and externalizing psychopathology[23-25]; this suggests that at least one of the CHRM2 SNPs must be a functional SNP. Since no SNP is present within the protein coding portion of the CHRM2 gene, the functional SNP must be exerting its effect by altering CHRM2 gene expression. It is difficult to envision a specific mechanism whereby SNPs present in the middle of a large intron (rs324650) or within downstream nontranscribed DNA (rs6962027, rs6967953, rs1378650, rs17506824) could strongly alter gene expression; however a specific mechanism is evident for the 3'UTR SNP rs8191992. This is because the rs8191992 T-allele improves a seed binding site for the brain-expressed microRNA hsa-mir-383 (Fig. 2c). In the

brain, M2 muscarinic receptors are primarily inhibitory presynaptic receptors, thus a decrease in their expression is expected to increase neurotransmitter release and synaptic transmission. Centrally acting M2 muscarinic antagonist drugs have been found to increase cognitive functioning in rodents and primates[26], and to increase vagal tone in rats[27]. By increasing the binding of hsa-mir-383, the rs8191992 T-allele would be expected to decrease expression of brain M2 muscarinic receptors and thereby cause increased cognitive functioning and increased vagal tone (Fig. 2d).

Ethnicity, CHRM2 allele frequency, systemic inflammation, and mortality

The CHRM2 vagal vigour hypothesis postulates that the lower cardiovascular and cancer mortality rates (Fig. 1h,i) seen in Hispanics, American Indians, and Asians are due in part to their higher frequencies of the rs8191992 T-allele (compared to Whites) and that the higher cardiovascular and cancer mortality in Blacks is due in part to their lower frequency of the rs8191992 T-allele. Two recent studies of ethnic differences in levels of systemic inflammation found that Asians tend to have lower levels and Blacks tend to have higher levels[28, 29], these data (median C-reactive protein levels in middle aged women) are displayed here (Fig. 2f) for comparison with ethnic variations in rs8191992 A-allele frequencies (Fig. 2e) and late middle age natural cause mortality (Fig. 2g). When viewed from the perspective of the CHRM2 vagal vigour hypothesis the lower mortality of Hispanics is not paradoxical and in this respect the Hispanic Health Paradox can be resolved. However then the lower IQs (Fig. 1 and Supplementary Fig. 1 & 2) and the higher rates of alcohol-related diseases (Supplementary Fig. 6) seen in Hispanics and American Indians remain as discrepancies within the CHRM2 vagal vigour model since these populations appear to have high levels of the T-allele (Fig.

2a,b) even though prior studies have associated the T-allele with higher IQ and lower

alcoholism[18, 20, 23, 24].

Discussion

The rs8191992 A-allele was associated with depression[30], lower IQ[18, 20], and lower

vagal tone[21, 22], this in combination with the vagal cholinergic anti-inflammatory

pathway[16] and the connection of inflammation with atherosclerosis[31], may explain why

depression is often associated with low IQ, low vagal tone, and increased systemic

inflammation and cardiovascular disease[32-36]. Variation in the CHRM2 3'UTR SNP

rs8191992 has also been associated with alcoholism/drug abuse[23, 24], and externalizing

psychopathology[25]. Thus in a more general sense, the CHRM2 vagal vigour hypothesis

postulates that the presence of the A-allele of rs8191992 may underlie the

epidemiological clustering of low IQ (and subsequent low SEP) and low vagal tone with

higher substance abuse, externalizing psychopathology, depression, systemic

inflammation, metabolic syndrome, and cardiovascular disease. Consistent with this

model, low vagal tone has been associated with lower indices of cognition (reaction

times, executive functions, working memory, and IQ)[17, 37, 38] and lower SEP[39]. Lower

vagal tone has also been associated with increased all cause mortality[40], cardiovascular

disease[41], type-2 diabetes/metabolic syndrome[42], major depression[33,35], alcoholism[43],

and externalizing psychopathology[44]. Furthermore, because low vagal tone has been

linked to higher levels of systemic inflammation[16, 45-47] and because inflammation has

been linked to the development of major aging-related diseases such as

atherosclerosis[31], type-2 diabetes/metabolic syndrome[48], and cancer[49], it is plausible that

vagal nerve signalling could be an important general regulator of health and longevity. Consistent with this notion, a widely used experimental anti-aging protocol—caloric restriction in rats—was found to be associated with activation of vagal tone[50]. The CHRM2 vagal vigour hypothesis raises the possibility that molecules that inhibit brain M2 muscarinic receptors might increase cognitive ability, vagal tone, and health and longevity, particularly in persons who are homozygous for the rs8191992 A-allele.

To summarize, this CHRM2 vagal vigour model posits that the derived T-allele of the CHRM2 3'UTR SNP rs8191992 improves a seed binding site for the brain-expressed microRNA hsa-mir-383 thus decreasing brain expression of M2 muscarinic receptors which leads to increased cognition, increased vagal tone, and better health. This may help to explain some previously puzzling associations of cognitive ability and SEP with ethnicity, vagal tone, systemic inflammation, and health. The mortality of Hispanics is lower than expected in view of their low SEP, this is known as the Hispanic Health Paradox[14]. It appears that Hispanics, due to Native American ancestry, have a low frequency (0.33) of the low vagal tone-associated A-allele of rs8191992; this may account for the low Hispanic mortality rates. The CHRM2 vagal vigour hypothesis offers an explanation for why the rs8191992 A-allele frequencies in Blacks (0.86), Whites (0.56), and East Asians (0.12) correspond with the respective ethnic differences in systemic inflammation[28, 29] and mortality[2](Fig. 2d,e,f,g). Lastly, by postulating a common shared link to the presence of the rs8191992 A-allele, the CHRM2 vagal vigour model provides an explanation for why low IQ, low SEP, low vagal tone, depression, substance abuse, externalizing psychopathology, systemic inflammation, type 2 diabetes/metabolic syndrome, and cardiovascular disease often cluster together.

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Figure Legends:

Figure 1 Cognitive epidemiology of ethnic populations comparing IQ, SEP, and mortality (age 55-64, yearly deaths per 100,000). **a,** Scatter-plot of IQ versus SEP of each area zone's total population. **b,** SEP versus mortality (♦ all cause, ♦ natural cause) of total population. **c,** IQ versus mortality (♦ all cause, ♦ natural cause) of total population. **d,** IQ versus SEP of each area zone's ethnic populations. **e,** SEP versus natural cause mortality of ethnic populations. **f,** IQ versus natural cause mortality of ethnic

populations. IQ (binned ethnic population data) compared with: **g,** natural cause mortality; **h,** cardiovascular disease mortality; and **i,** cancer mortality. **d-i,** ■ Black, ■ Hispanic, ■ American Indian, ■ White, ■ Asian. **g,h,i,** Error bars are 95% confidence intervals. Unfilled symbols are nationwide USA data. SEP estimates were from US Census 2000 data with SEP = $(P_{edu} + P_{inc}) \cdot 50$ where P_{edu} = fraction of adults age ≥ 25 with bachelor's degree or higher and P_{inc} = fraction of adults age 35-64 with annual household income of ≥ \$75,000. IQ estimates were derived using the Excel NORMINV function with IQ_{group} = NORMINV(P_{group},0,15) - NORMINV(P_{White},0,15) + 100 where P_{group} = fraction of group and P_{white} = fraction of statewide Whites who score proficient or above on California CST 7th grade maths (years 2003-2006; //star.cde.ca.gov). California mortality data (all deaths from years 1999-2005) were obtained from the CA Dept. of Public Health. SEP and mortality data, which were localized to ZipCode areas, were linked and aggregated to correspond to the area zones of the CST maths-derived IQ data. Larger empty symbols in **g-i** represent national NAEP 8th grade maths-derived IQ (years 2000, 2003, 2005, & 2007; //www.nces.ed.gov/nationsreportcard) and nationwide mortality (years 1997-2005 CDC NVSS database //www.cdc.gov/nchs/hdi.htm).

Figure 2 The CHRM2 vagal vigour hypothesis. **a,** Location of six SNPs in the 3-prime region of the CHRM2 gene. **b,** Ethnic allele frequencies at these six CHRM2 SNPs. **c,** Seed binding site interaction of microRNA hsa-miR-383 with the 3'UTR region of the CHRM2 mRNA. **d,** Schematic summary of the CHRM2 vagal vigour hypothesis. **e,** CHRM2 SNP rs8191992 A-allele frequencies of Hispanic, Black, White, and Asian populations. **f,** Systemic inflammation in ethnic populations, median serum C-reactive protein levels in middle aged women (█ ~55 years old[28], █ ~46 years old[29]). **g,** Natural cause mortality (age 55-64, yearly deaths per 100,000) in USA Nationwide ethnic populations. Ethnic group SNP allele frequencies for Whites, Blacks, and Asians are from the HapMap and Perlegen data and for Hispanics (Mexicans) are from HapMap data. The data set containing SNP allele frequencies for Indians (Native American groups Maya, Nahua, Quechua, and Aymara from Mexico, Bolivia, and Peru[15]) was obtained from Xianyun Mao and Mark Shriver. The CRP data are from Albert et al.[28] and Kelley-Hedgepeth et al.[29] The nationwide mortality data are from years 1997-2005 (CDC NVSS database //www.cdc.gov/nchs/hdi.htm).

a

1 rs324650 2 rs8191992 4 rs6967953 6 rs17506824
A/T A/T C/T C/T
CHRM2 gene
intron CDS 3'UTR A/T C/T
exon 3 rs6962027 5 rs1378650

b

Allele Frequency

	Asian	White	Black	Hispanic	Indian	N
1	514	424	808	94	208	
2	220	160	146	na	na	
3	220	160	146	na	na	
4	516	424	808	94	na	
5	222	160	156	na	208	
6	516	424	808	94	na	SNP

c

CHRM2 mRNA rs8191992 A-allele
5'...UCUCAUAAUCUCUUGAAGAAGGG CUUCUGA AUCUACA...3'
                            GAAGACU
hsa-miR-383 3' UCGGUGUUAGUG AGA5'

CHRM2 mRNA rs8191992 T-allele
5'...UCUCAUAAUCUCUUGAAGAAGGG CUUCUGAUU CUACA...3'
                            GAAGACUAG
hsa-miR-383 3' UCGGUGUUAGUG A5'

d

↑ hsa-miR-383
binding to 3'UTR ↓ M2 Muscarinic
receptor expression

↑ Cognitive Ability
↑ Math achievement
↑ Education level
↑ SEP

T-allele
SNP rs8191992

↑ Vagal Tone
(↑ HRV, HRR, RSA) Healthier
Behaviour

Frequency:
Asian – high(0.88)
White – mid(0.44)
Black – low(0.14)

↓ Systemic Inflammation
(↓ CRP, IL-6, TNF)

↑ Health &
Longevity

↓ Atherosclerosis & Cancer

e

A-allele frequency

H B W A

f

CRP (mg/L)

H B W A

g

Mortality

H B W A

% Below Basic
% Basic
% Proficient
% Advanced

60
50
40
30
20
10
0

39058	232845	3918	3175	3275	147252	12971	9558	3771	6425	2168	4639	10995
Black	Hispanic	American Indian	Pacific Islander	Laotian or Cambodian	White	Filipino	Other Asian	Asian Indian	Viet-namese	Japanese	Korean	Chinese
85.4	88.2	90.4	91.6	93.7	100.0	100.0	101.6	103.2	106.6	109.6	111.9	112.5

Supplementary Figure 1 Statewide scores from the 2006 7th Grade Mathematics California Standards Test (CST). Shown are the number tested from each ethnic group and the standard score (IQ metric) derived from the fractions Proficient or Advanced by using the Excel NORMINV function with $IQ_{group} = NORMINV(P_{group},0,15) - NORMINV(P_{White},0,15) + 100$ where P_{group} − fraction of group and P_{white} − fraction of statewide Whites who score proficient or above on the California CST 7th grade mathematics test. (data source http://star.cde.ca.gov/star2006/Viewreport.asp).

	2003	2004	2005	2006	ave	2003	2004	2005	2006	ave	2003	2004	2005	2006	ave	2003	2004	2005	2006	ave	2003	2004	2005	2006	ave
N	41872	41255	39403	39058		215852	225251	226202	232845		4522	4170	4093	3918		170962	163787	155365	147252		51479	52539	53115	53800	
IQ	84.6	84.5	86.1	85.4	85.2	87.3	87.0	88.2	88.2	87.7	90.2	91.1	90.9	90.4	90.6	100.0	100.0	100.0	100.0	100.0	104.4	104.5	105.1	104.3	104.6
			Black					Hispanic				American Indian						White					Asian		

Supplementary Figure 2 Statewide scores from 2003-2006 on the 7th Grade Mathematics California Standards Test (CST). Shown are the number tested each year from each ethnic group and the standard score (IQ metric) derived from the fractions Proficient or Advanced by using the Excel NORMINV function with $IQ_{group} = NORMINV(P_{group},0,15) - NORMINV(P_{White},0,15) + 100$ where P_{group} – fraction of group and P_{white} – fraction of statewide Whites who score proficient or above on the California CST 7th grade mathematics test. The final estimate is the average of the values for each of the four years.
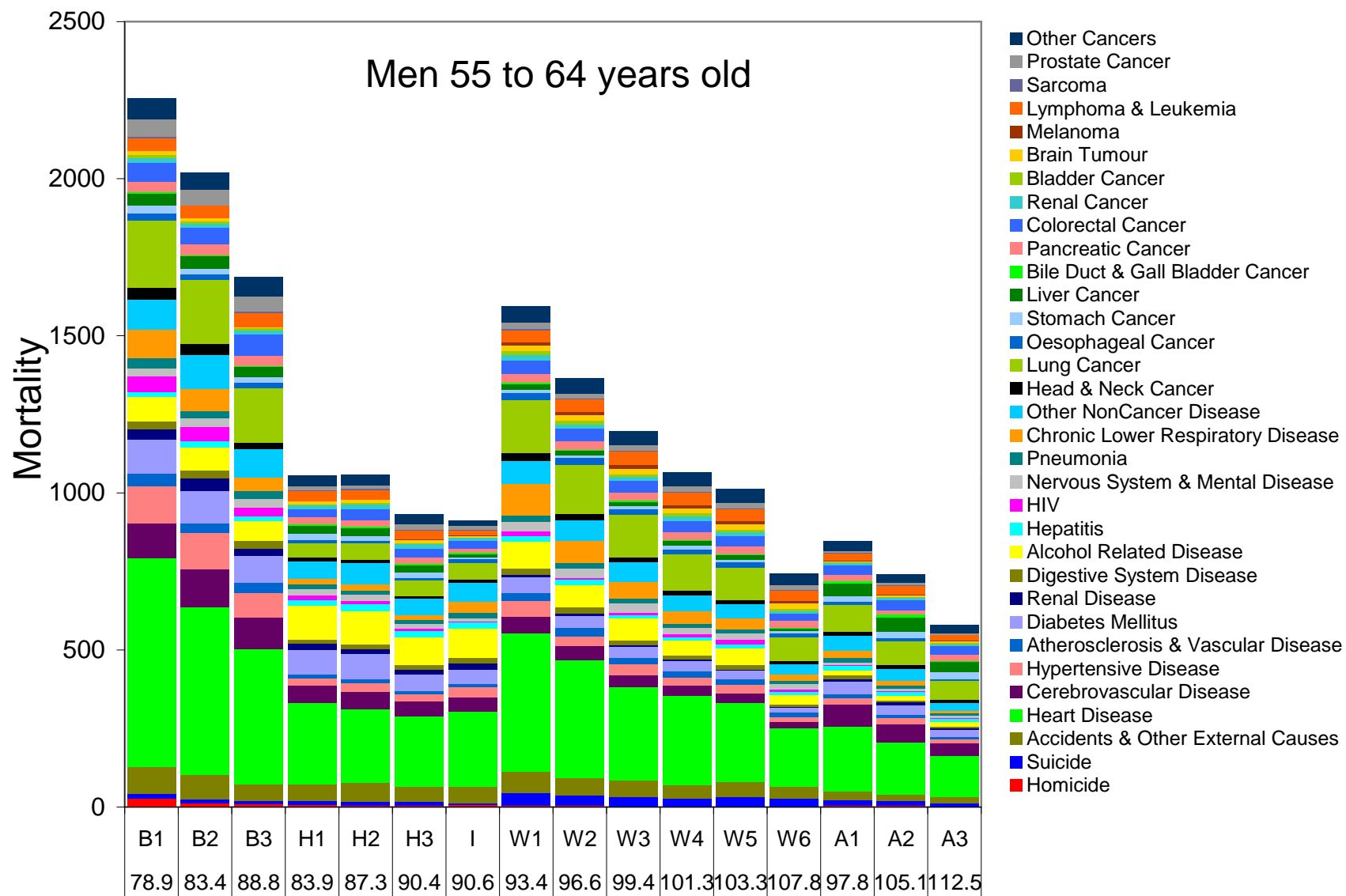
Supplementary Figure 3 Proportions of mortality (yearly deaths per 100,000) in men due to various specific causes. IQ-binned data from geographic area populations of Blacks, Hispanics, American Indians, Whites, and Asians.
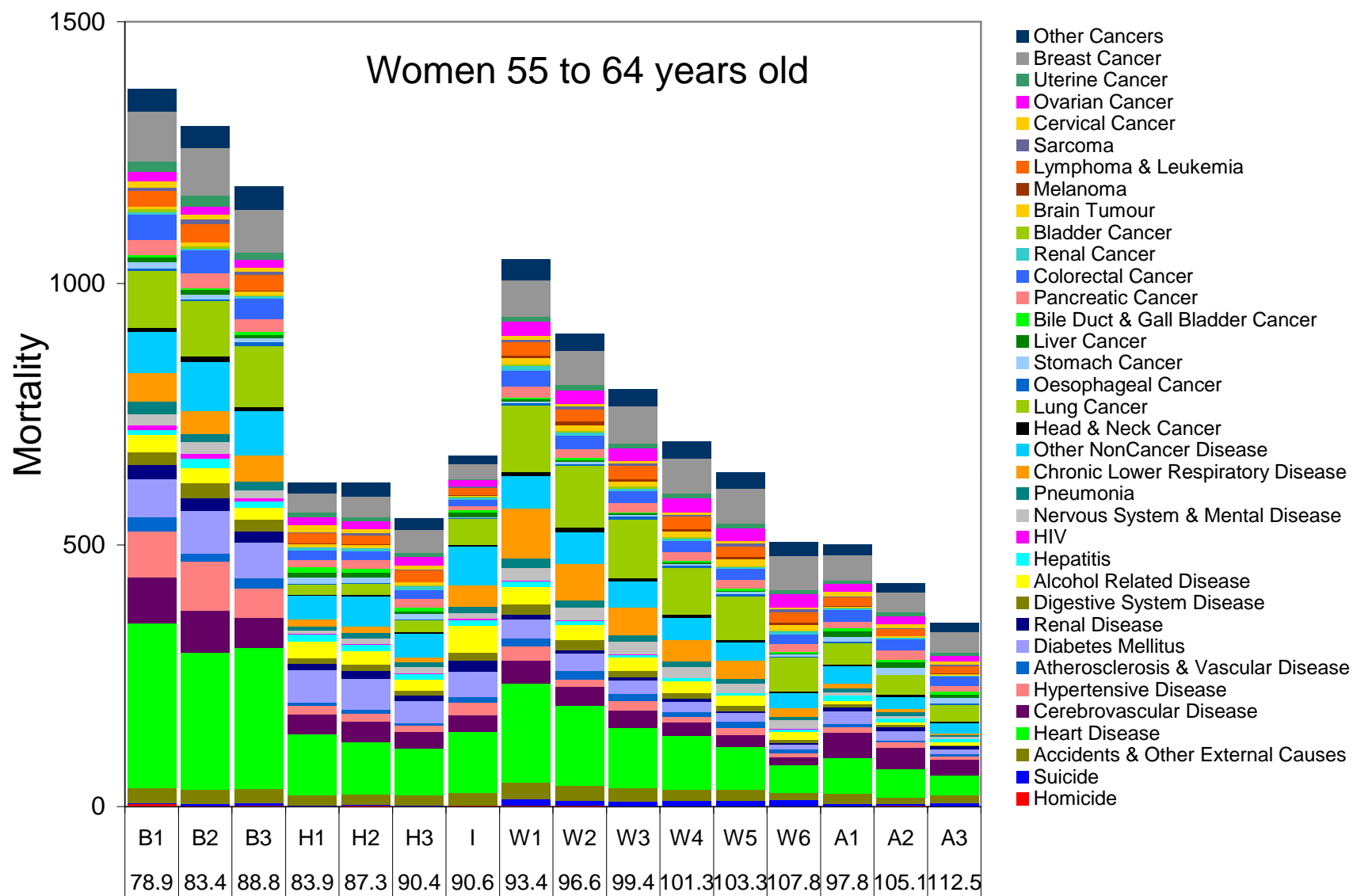
Supplementary Figure 4 Proportions of mortality (yearly deaths per 100,000) in women due to various specific causes. IQ-binned data from geographic area populations of Blacks, Hispanics, American Indians, Whites, and Asians.

External Cause (V01-Y89):
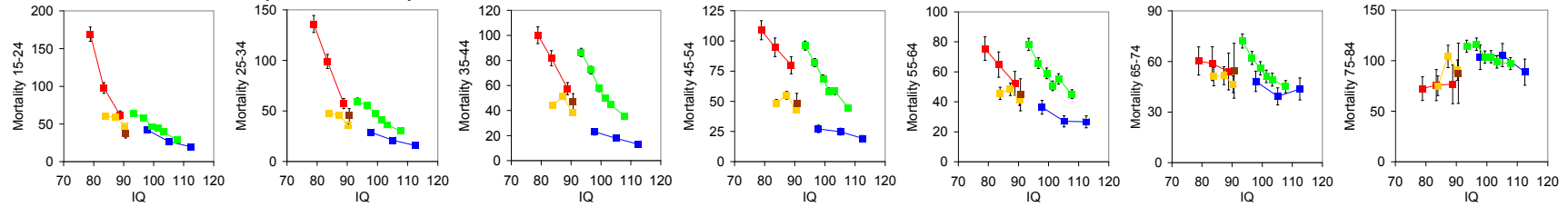
Accidents (V01-X59,Y85-Y86):
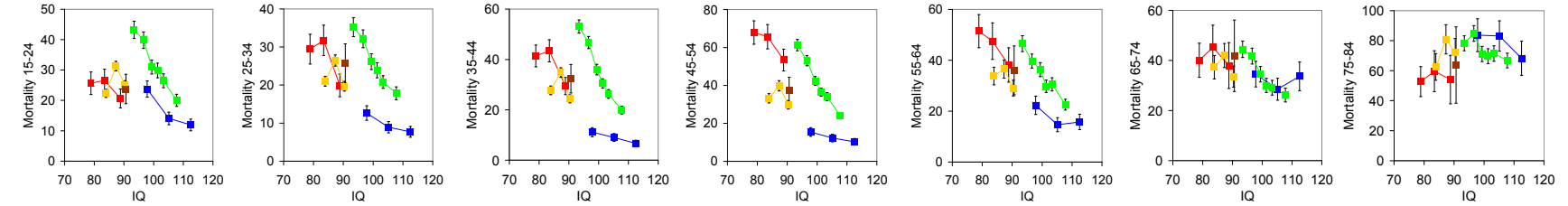
Homicide (X85-Y09,Y87.1):
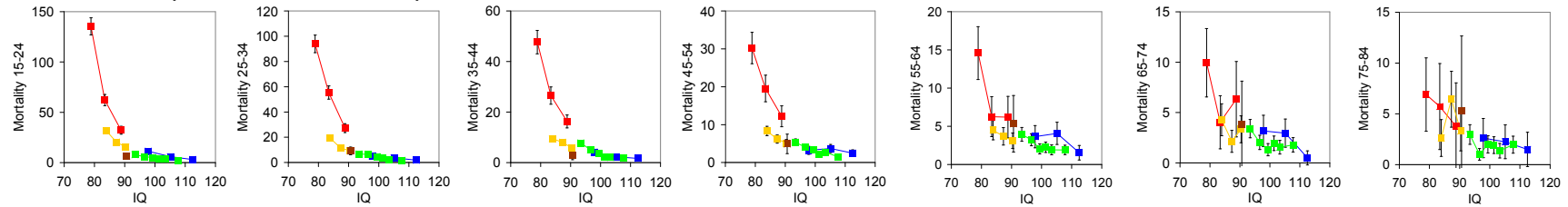
Suicide (X60-X84,Y87.0):
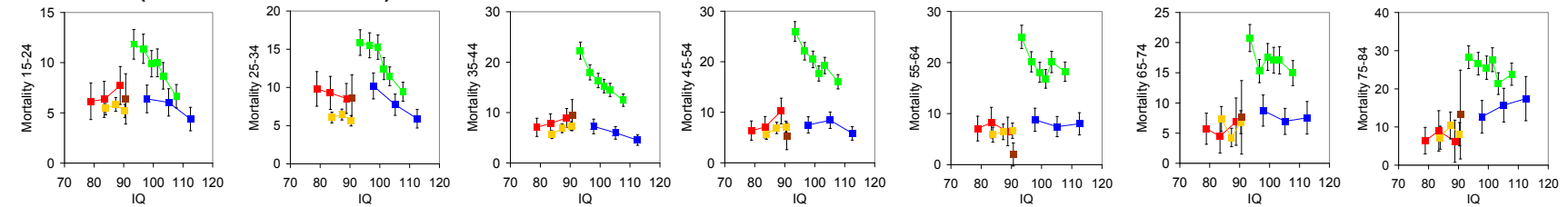
Supplementary Figure 5 Cognitive epidemiology of mortality (yearly deaths per 100,000) in California due to external causes at various ages in relation to IQ and ethnicity. ■ Black, ■ Hispanic, ■ American Indian, ■ White, ■ Asian. Error bars are 95% confidence intervals. (ICD10 Group Cause of Death Codes).

Heart Disease (I20-I25,I27,I28,I30-I51):
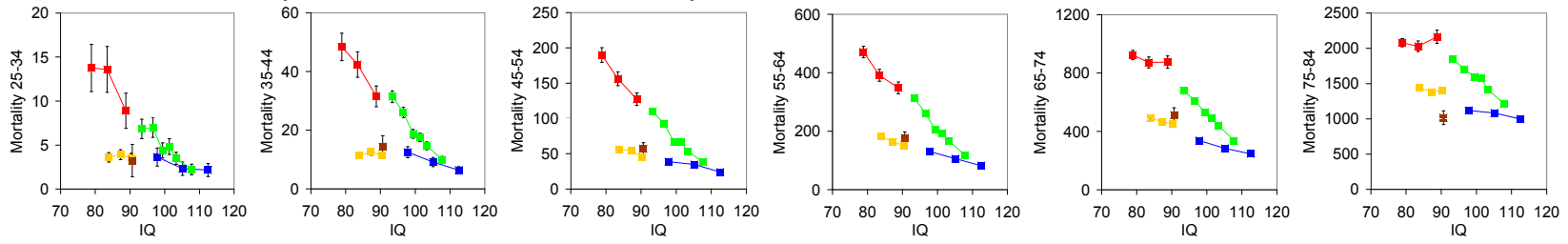
Cerebrovascular Disease (I60-I69):
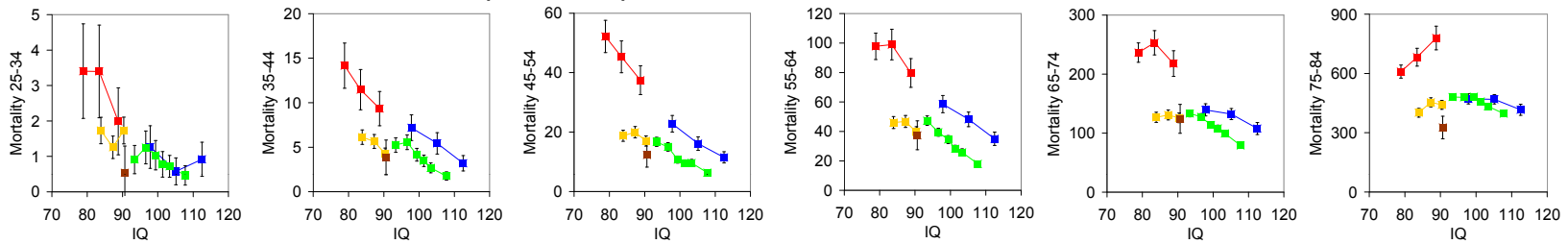
Hypertension (I10-I13):
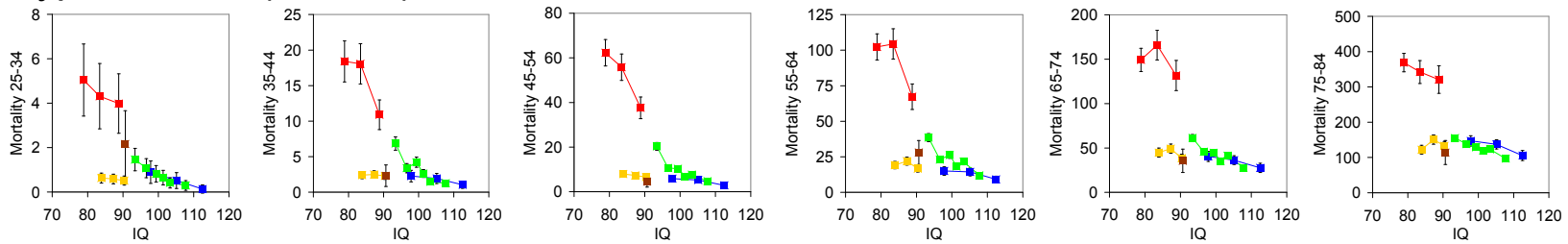
Other Atherosclerosis and Vascular Disease (I26,I70-I78,I80-I99):
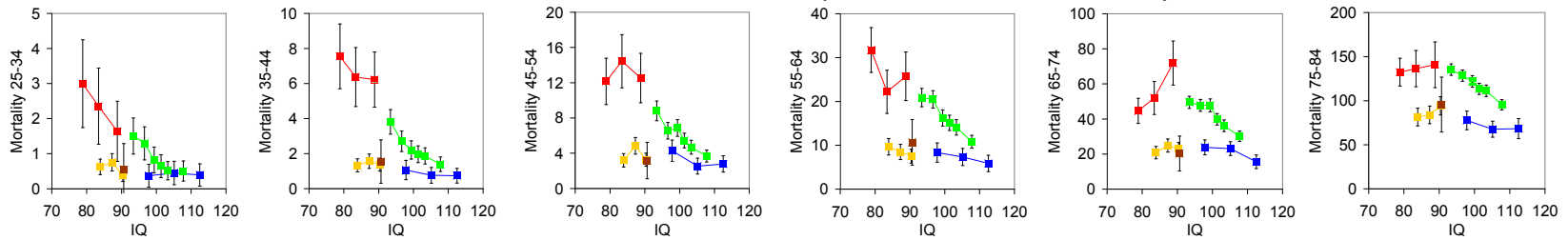
Renal Disease (N01-N07,N10-N15,N17-N27):
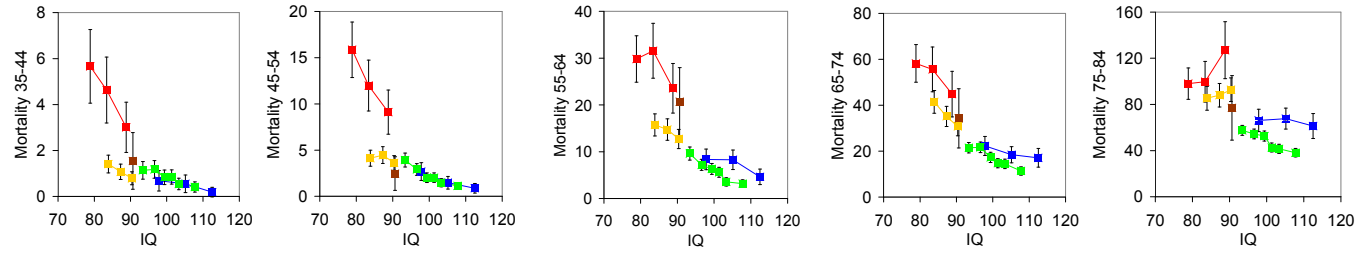
Diabetes Mellitus (E10-E14):
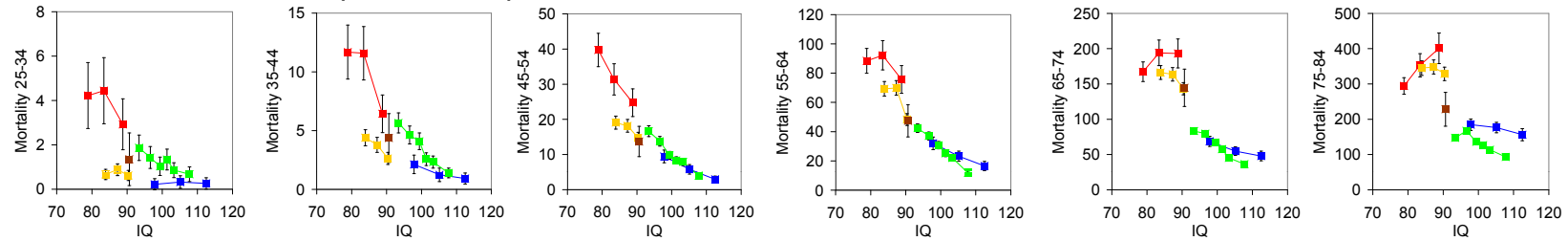
Chronic Lower Respiratory Diseases (J40-J47):
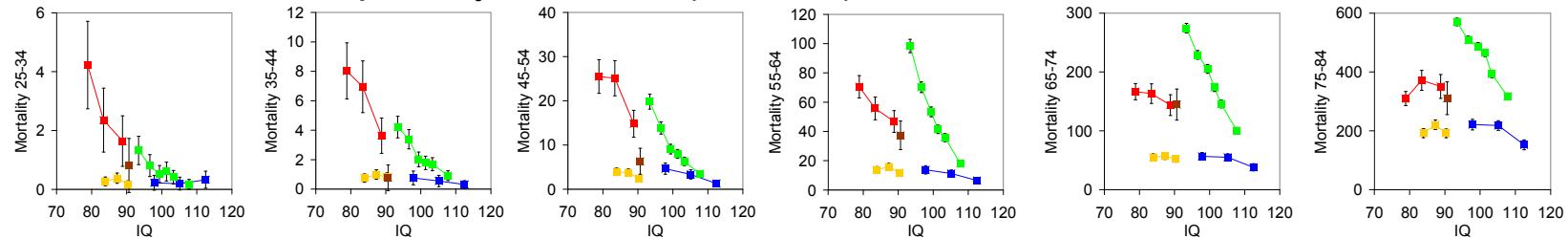
Pneumonia (J10-J22):
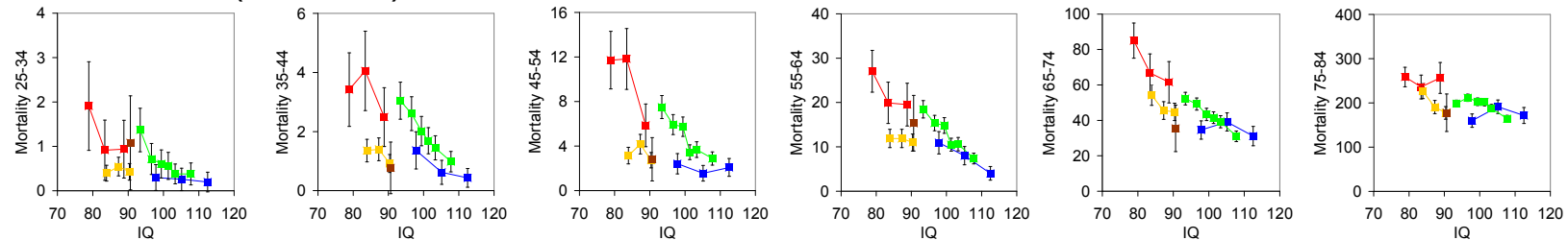
Alcohol Related Diseases (F10,K70,K74,K85,K86.1-K86.2):
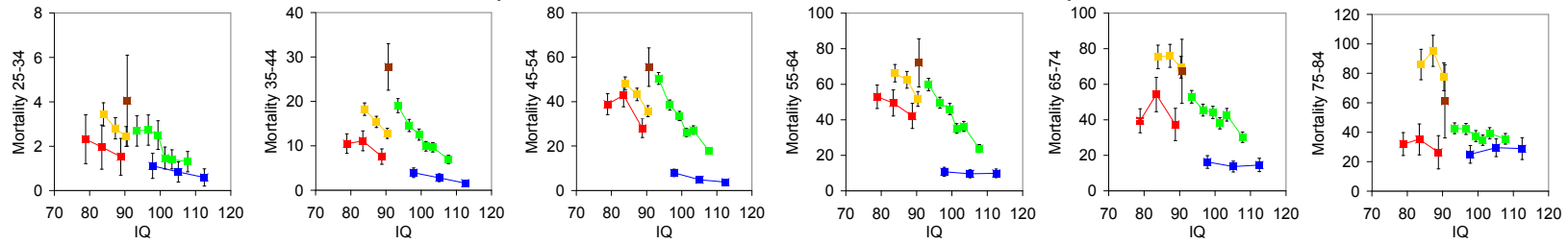
HIV (B20-B24):
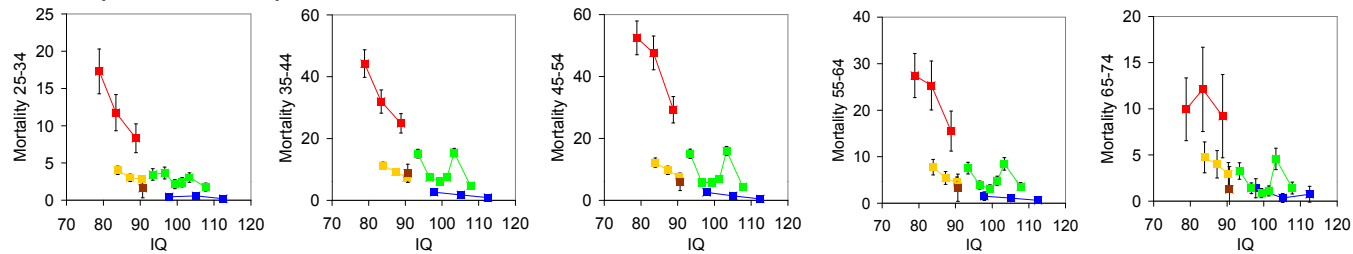
Hepatitis (B15-B19,K71-K76):
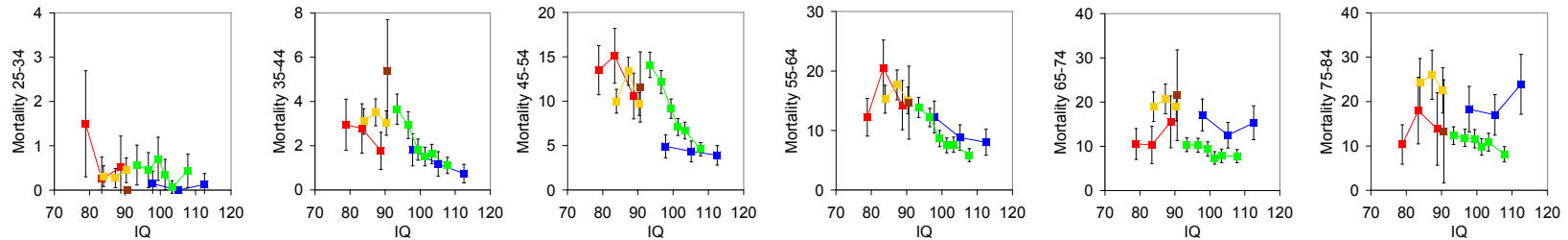
Digestive System Diseases (K20-K66,K80-K83,K86.2-K86.9):
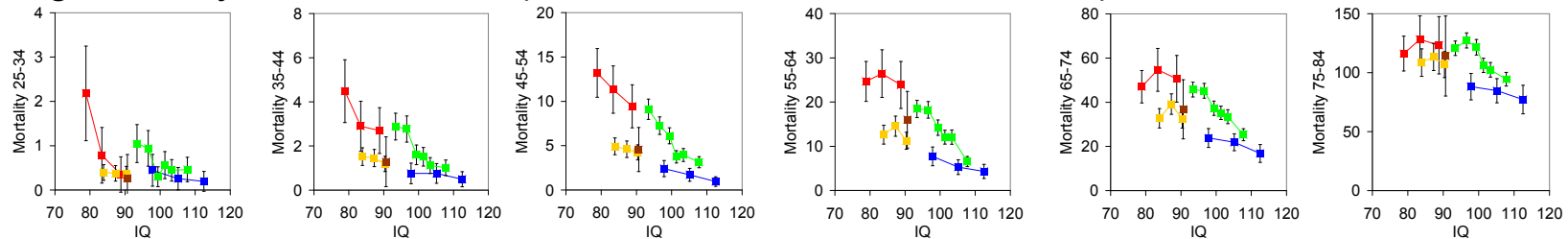
Nervous System & Mental Diseases (F01-F09,F11-F99,G00-G37):
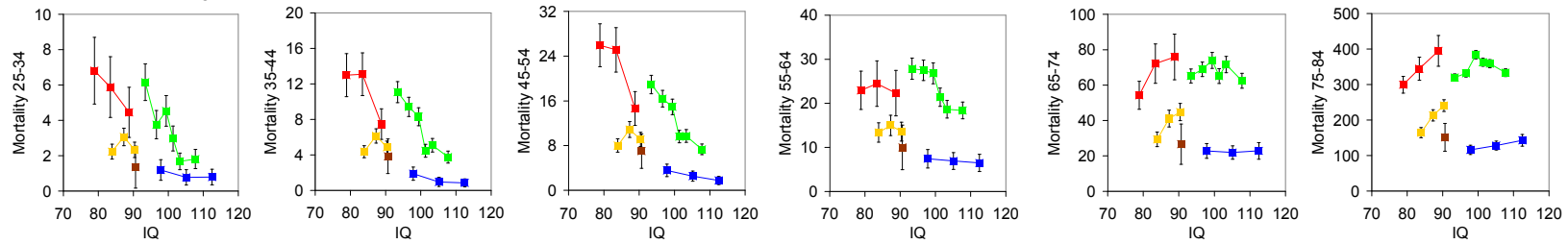
Supplementary Figure 6 Cognitive epidemiology of mortality (yearly deaths per 100,000) in California due to noncancer natural causes at various ages in relation to IQ and ethnicity. ■ Black, ■ Hispanic, ■ American Indian, ■ White, ■ Asian. Error bars are 95% confidence intervals. (ICD10 Group Cause of Death Codes).

All Cancer (C00-C97,D00-D48):
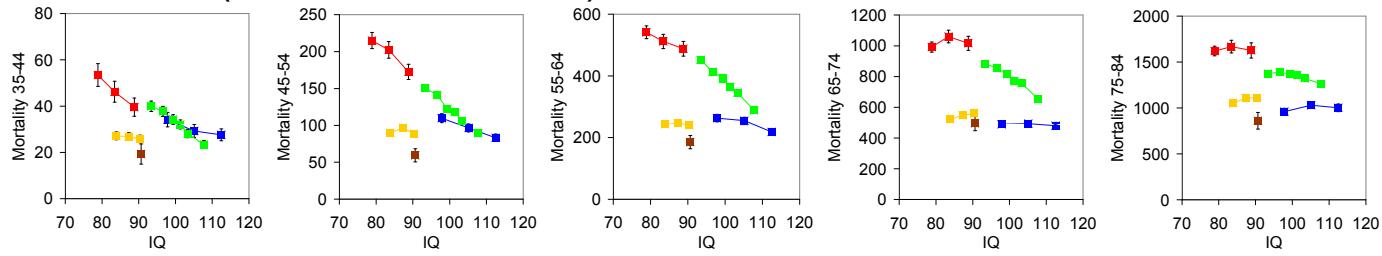
Lung Cancer (C33,C34):
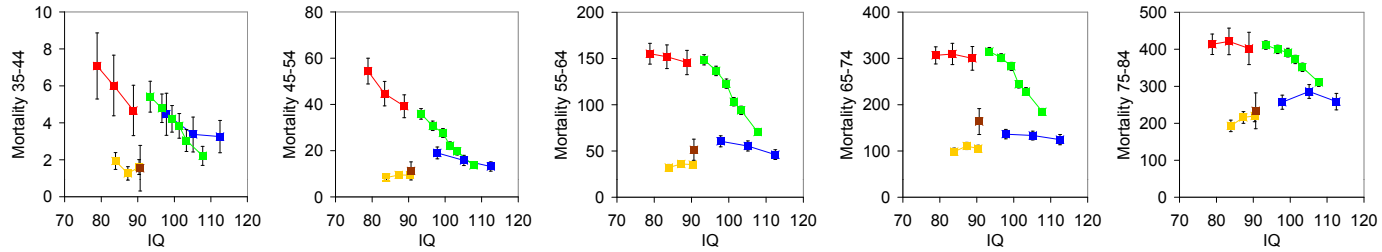
Colorectal Cancer (C18-C20):
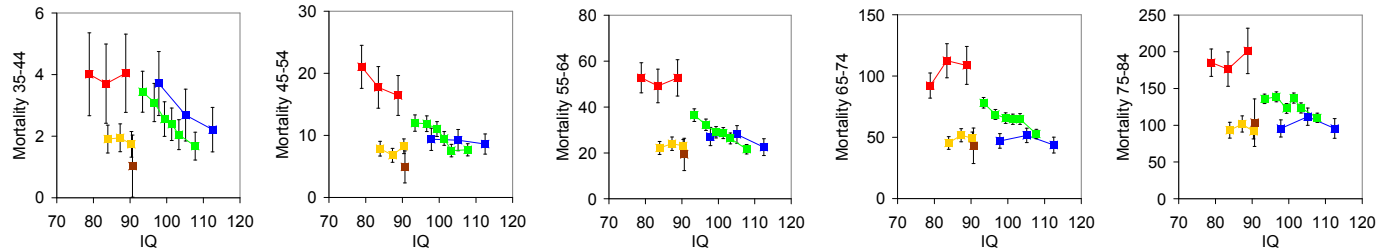
Pancreatic Cancer (C25):
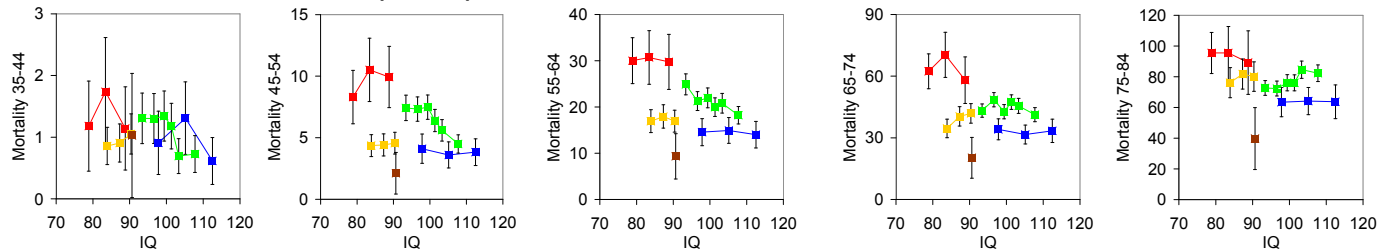
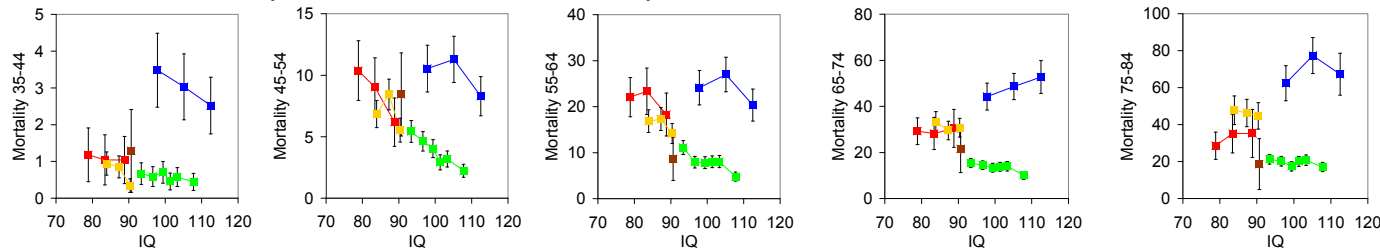## Head & Neck Cancer (C00-C14,C30-C32):
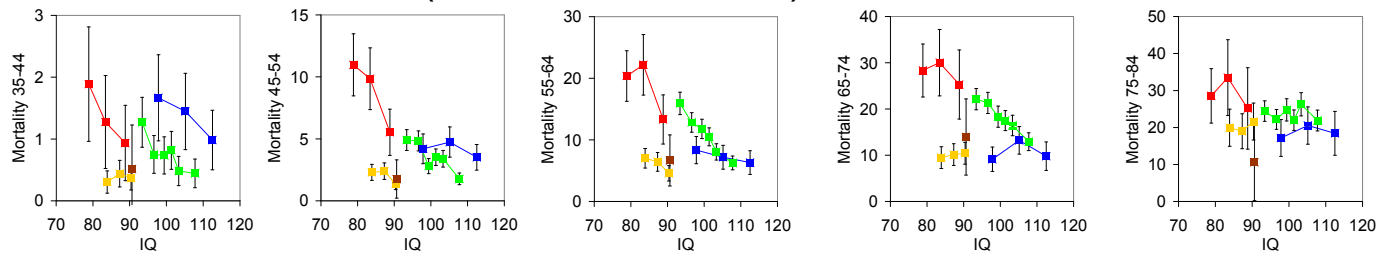
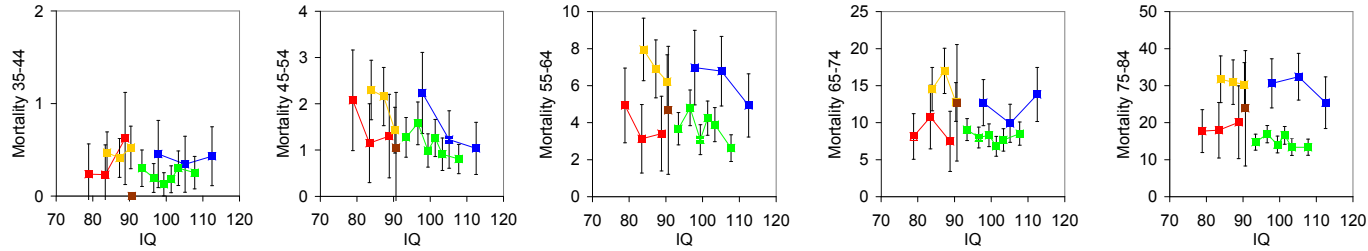## Oesophageal Cancer (C15):
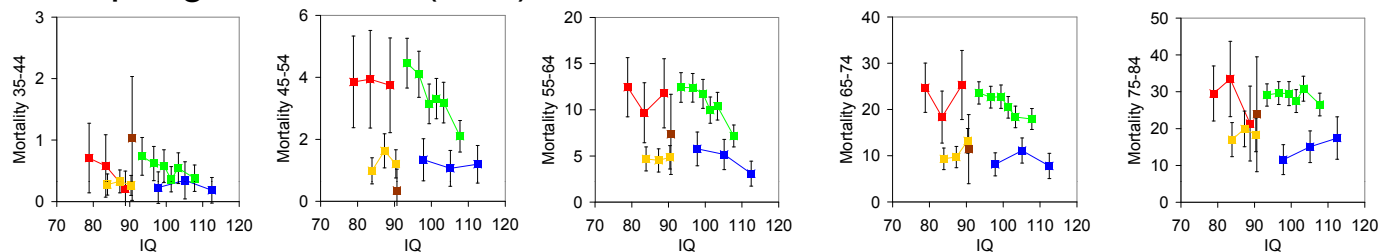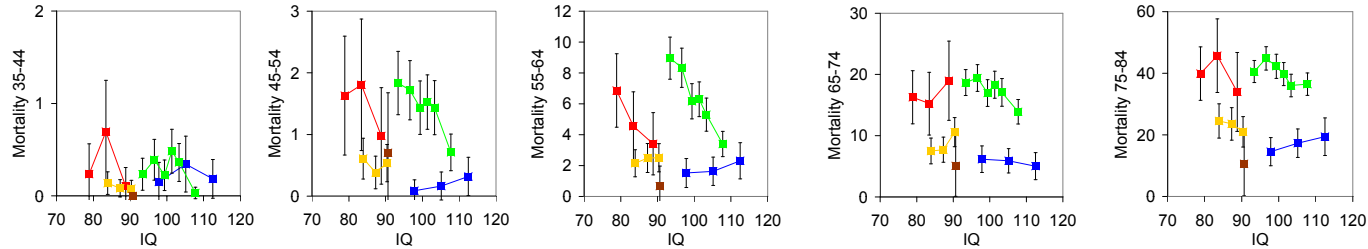

Stomach Cancer (C16):
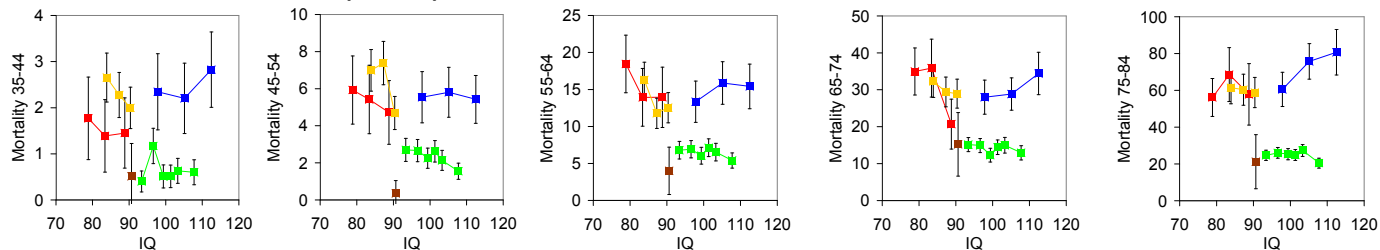
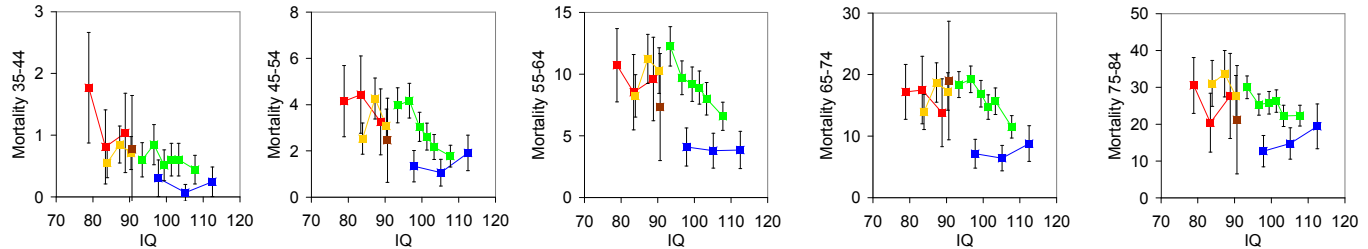## Liver Cancer (C22.0,C22.2-C22.9):
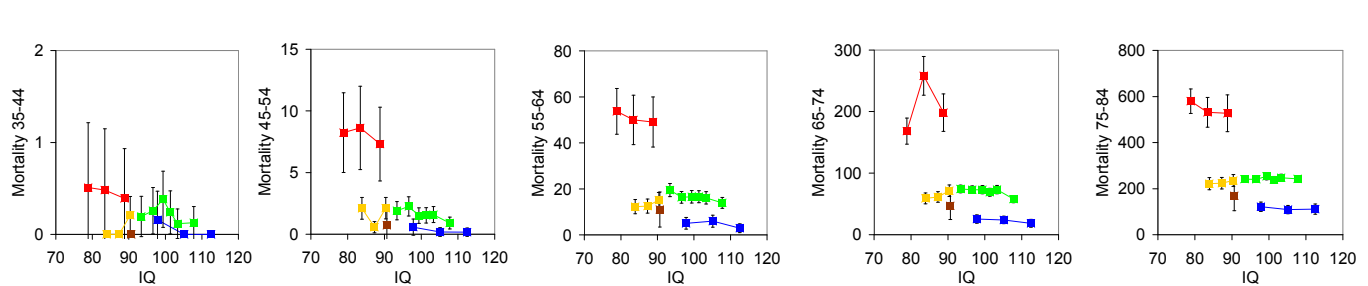
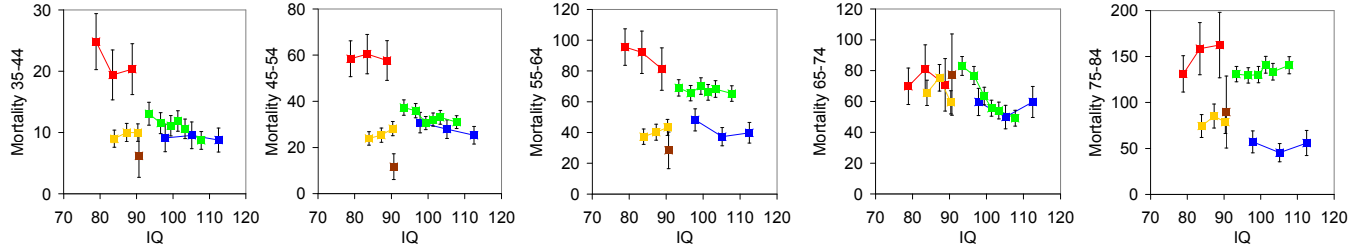## Biliary Cancer (C22.1,C23-C24):

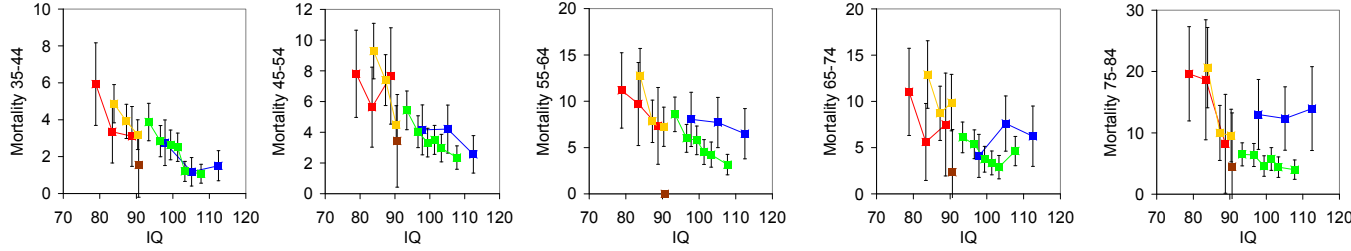## Bladder Cancer (C67):

Renal Cancer (C64-C65):

Prostate Cancer (C61):

Breast Cancer (C50):

Cervical Cancer (C53):

Ovarian Cancer (C56):
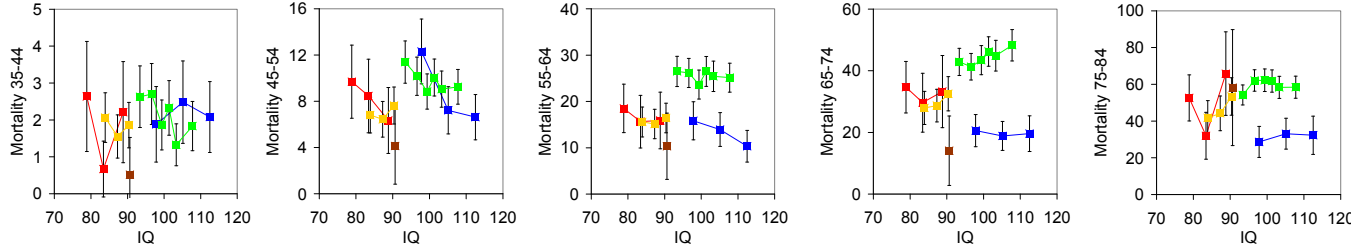
Uterine Cancer (C54,C55):
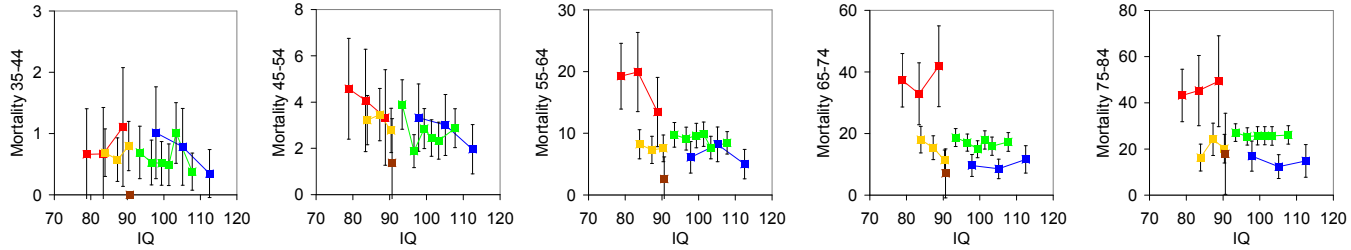
Melanoma (C43):
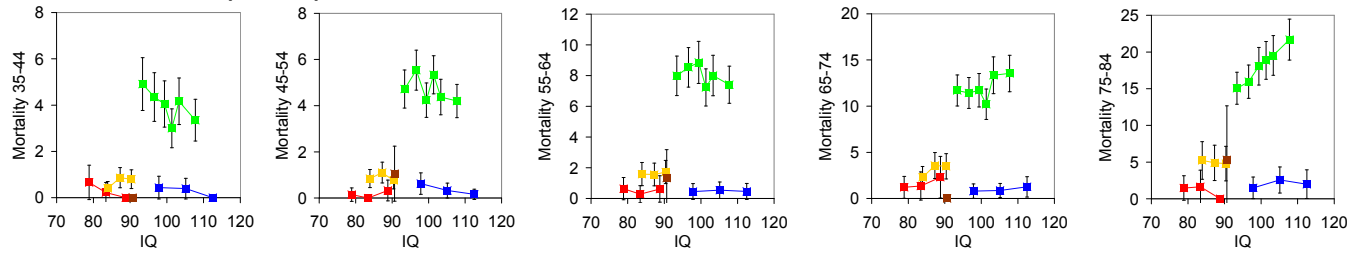
Brain & CNS Neoplasm (C70-C72):
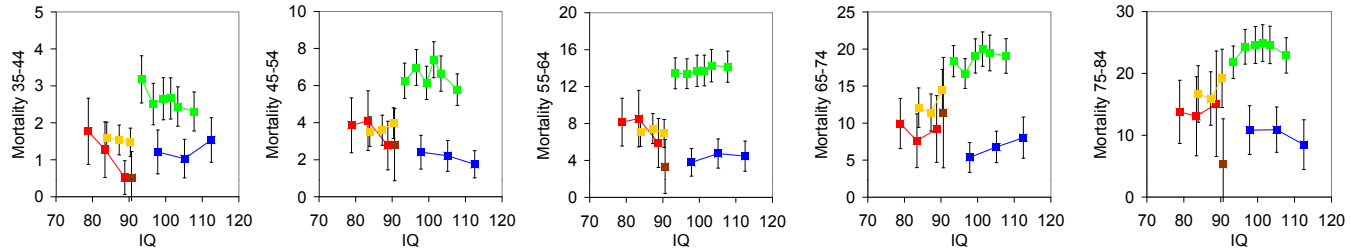
Sarcoma (C40,C41,C47-C49):
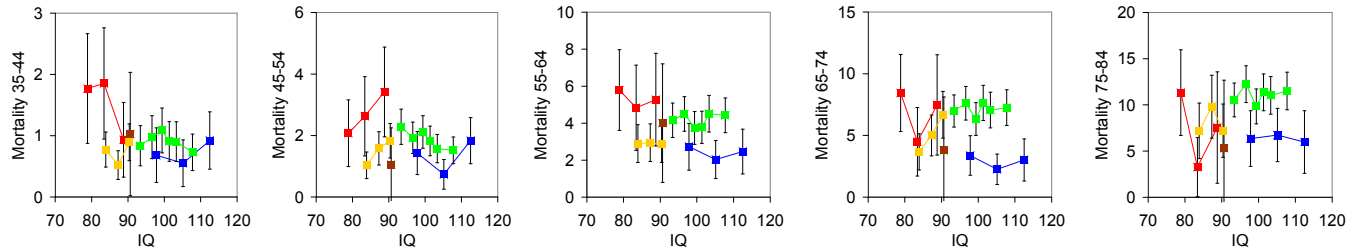
Lymphoma & Leukemia (C81-C96):
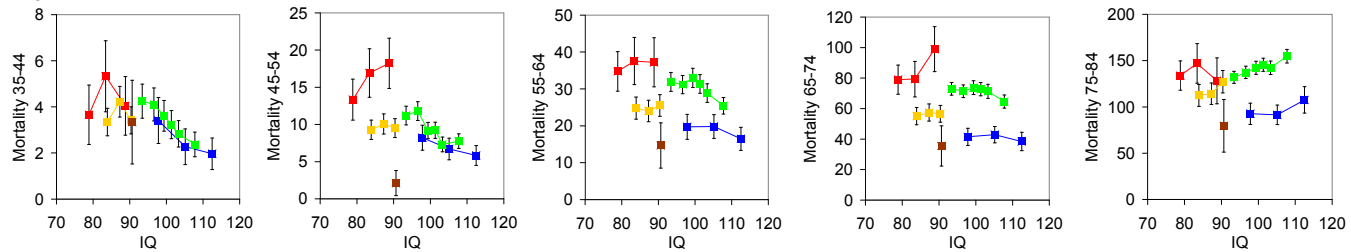
All Cancer [15-24 & 25-34 Age Groups] (C00-C97,D00-D48):
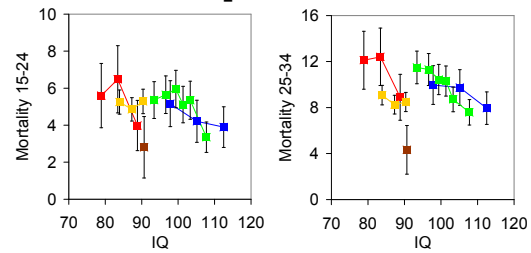
Supplementary Figure 7 Cognitive epidemiology of mortality (yearly deaths per 100,000) in California due to cancer at various ages in relation to IQ and ethnicity. ■ Black, ■ Hispanic, ■ American Indian, ■ White, ■ Asian. Error bars are 95% confidence intervals. (ICD10 Group Cause of Death Codes).

a

NM_001006632
CHRM2: cholinergic receptor, muscarinic 2

rs324637 rs420817 rs324640 rs324650 rs8191992 rs6962027 rs6967953 rs1378650 rs10246819 rs17506824

Asian
 (Japanese & Chinese)

LD Plot

Block 1 (6 kb)   Block 2 (8 kb)

Haplotype frequencies

```
028 029 031 045                    063 066 069 072 079 082
ACGT .911 ———— TTTTTT .844
TTAA .050 ⤬        AACCCC .128
ACGA .019         TACCCC .011
ACAA .019
                              .77
```

b

NM_001006632
CHRM2: cholinergic receptor, muscarinic 2

rs324637 rs420817 rs324640 rs324650 rs8191992 rs6962027 rs6967953 rs1378650 rs10246819 rs17506824

White

LD Plot

Block 1 (14 kb)   Block 2 (7 kb)

Haplotype frequencies

```
028 029 030 044 062            065 068 071 078 081
TTAAA .491 ———— ACCCC .500
ACGTT .400 ⤬      TTTTT .392
ACGTA .067        ACTCC .042
ACAAT .022        TCCTT .050
ACGAT .011
                          .86
```

c
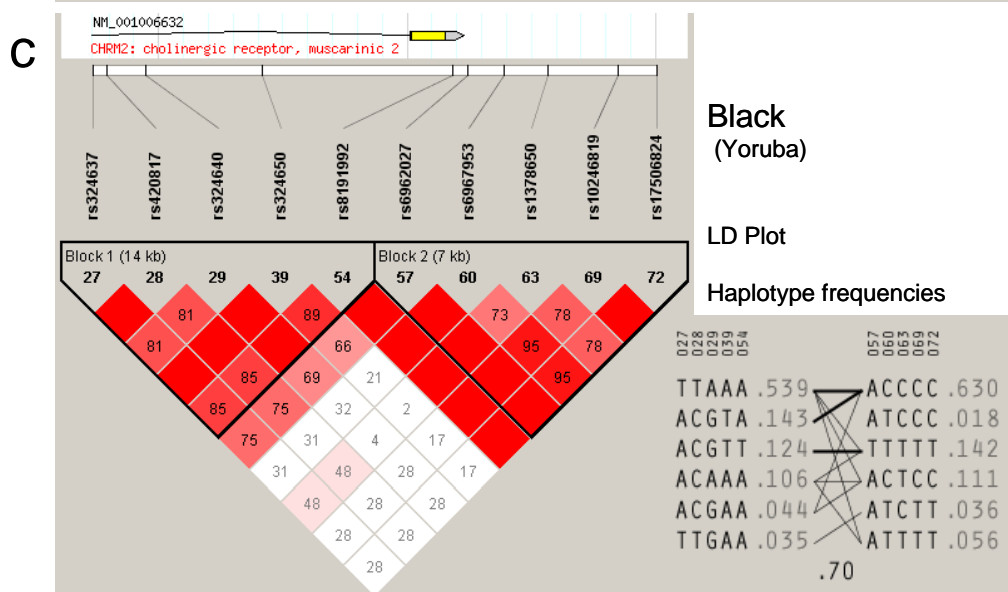
NM_001006632
CHRM2: cholinergic receptor, muscarinic 2

rs324637 rs420817 rs324640 rs324650 rs8191992 rs6962027 rs6967953 rs1378650 rs10246819 rs17506824

Black
 (Yoruba)

LD Plot

Block 1 (14 kb)   Block 2 (7 kb)

Haplotype frequencies

```
027 028 029 039 054            057 060 063 069 072
TTAAA .539 ———— ACCCC .630
ACGTA .143        ATCCC .018
ACGTT .124        TTTTT .142
ACAAA .106        ACTCC .111
ACGAA .044        ATCTT .036
TTGAA .035        ATTTT .056
                          .70
```

Supplementary Figure 8 CHRM2 gene Linkage Disequilibrium (LD) plots and haplotype frequencies of ethnic groups. **a,** Asians (Japanese and Chinese). **b,** Whites. **c,** Blacks (Yoruba). Data are from the HapMap (http://www.hapmap.org/) and were processed using the HaploView program.

Controversy regarding ethnic group differences
Nature vs. Nurture

Galtonians	Boasians
Hereditarians / Essentialists	**Environmentalists / Behaviourists**
Georges Cuvier (1769-1832)	(1786-1948) James Prichard
William Edwards (1776-1842)	(1821-1902) Rudolf Virchow
Robert Knox (1793-1862)	(1826-1905) Adolf Bastian
Samuel Morton (1799-1851)	(1850-1927) Léonce Manouvrier
Francis Galton (1822-1911)	**(1858-1942) Franz Boas**
Herbert Spencer (1820-1903)	(1878-1958) John B. Watson
Paul Broca (1824-1880)	(1904-1990) B.F. Skinner
Ernst Haeckel (1834-1919)	(1895-1963) Melville Herskovits
G. Vacher de Lapouge (1854-1936)	(1887-1948) Ruth Benedict
Otto Ammon (1842-1916)	(1901-1978) Margaret Mead
Karl Pearson (1857-1936)	(1899-1992) Otto Klineberg
Charles Spearman (1863-1945)	(1898-1987) K. Gunnar Myrdal
Cyril Burt (1883-1971)	(1897-1967) Gordon Allport
Henry Garrett (1894-1973)	(1905-1972) Horace Mann Bond
Earnest Hooton (1887-1954)	(1905-1999) Ashley Montagu
Carleton Coon (1904-1981)	(1911-2000) Sherwood Washburn
Philip E. Vernon (1905-1987)	(1922-) L. Luca Cavalli-Sforza
Raymond Cattell (1905-1998)	(1929-) Richard Lewontin
Audrey Shuey (1910-1977)	(1928-) Leon Kamin
Lloyd Humphreys (1913-2003)	(1930-) C. Loring Brace
Hans Eysenck (1916-1997)	(1934-) James Flynn
Arthur Jensen (1923-)	(1936-) Christopher Jencks
Richard Lynn (1930-)	(1936-) Abigail Thernstrom
Vincent Sarich (1934-)	(1937-) Jared Diamond
Thomas Bouchard (1937-)	(1938-) Steven Rose
Richard Herrnstein (1930-1994)	(1941-2002) Stephen Jay Gould
Charles Murray (1943-)	(1942-) Ned Block
Chris Brand (1943-)	(1941-) Richard Nisbett
Michael Levin (1943-)	(1943-) Howard Gardner
J. Philippe Rushton (1943-)	(1946-) Claude Steele
Linda Gottfredson (1947-)	(1948-) Claude Fischer
David Rowe (1949-2003)	(1949-) Robert Sternberg
Henry Harpending (1944-)	(1954-) Eric Turkheimer
James Watson (1928-)	(1955-) Jonathan Marks
Steven Pinker (1954-)	(1955-) Joseph Graves
Satoshi Kanazawa (1962-)	(1958-) Nancy Krieger

Supplementary Table 1

Study	N	IQ-increaser allele		Δ IQ (TT versus AA genotype)	Cohort
		rs324650	rs8191992		
Comings et al. 2003*	828	–	T*	+4.1 (FSIQ)	Minnesota Twin & Family Study
Gosso et al. 2006	191	T	–	+8.2 (FSIQ)	Netherlands Twin Registry (Family-based comparison)
	625	T	–	+3.4 (FSIQ)	Netherlands Twin Registry (Population-based comparison)
Dick et al. 2007*	2158	–	T*	+4.9 (PIQ)	Collaborative Study on the Genetics of Alcoholism (COGA)
Harris et al. 2007	437	–	No effect found	No effect found	Lothian Birth Cohort of 1921

* **IMPORTANT NOTE**: With regard to the studies by Comings et al. 2003 and Dick et al. 2007, the published reports are ambiguous and confusing as per how their reported alleles of rs8191992 correspond with the SNP database-designated A and T alleles of rs8191992. This was clarified by personal communications from David Comings (their "allele 1" = dbSNP A allele and their "allele 2" = dbSNP T allele) and from Danielle Dick (because a reverse primer was used in their pyrosequencing assay, their "A allele" = dbSNP T allele and their "T allele" = dbSNP A allele). Here the dbSNP allele designations are shown.

Comings, D. E. et al. Role of the cholinergic muscarinic 2 receptor (CHRM2) gene in cognition. *Mol. Psychiatry* **8**, 10-11 (2003).

Gosso, M. F. et al. Association between the CHRM2 gene and intelligence in a sample of 304 Dutch families. *Genes Brain Behav.* **5**, 577-584 (2006).

Dick, D. M. et al. Association of CHRM2 with IQ: converging evidence for a gene influencing intelligence. *Behav. Genet.* **37**, 265-272 (2007).

Harris, S. E. et al. A genetic association analysis of cognitive ability and cognitive ageing using 325 markers for 109 genes associated with oxidative stress or cognition. *BMC Genet.* **8,** 43 (2007).

Supplementary Table 2