GLOBAL HEART VOL. 7, NO. 4, 2012

ISSN 2211-8160/$36.00
http://dx.doi.org/10.1016/j.gheart.2012.10.003

gSCIENCE

ORIGINAL RESEARCH

Assessing the Global Burden of Ischemic Heart Disease

Part 2: Analytic Methods and Estimates of the Global Epidemiology of Ischemic Heart Disease in 2010

Mohammad H. Forouzanfar [*], Andrew E. Moran [†], Abraham D. Flaxman [*], Gregory Roth [*,‡], George A. Mensah [§], Majid Ezzati [*,||], Mohsen Naghavi [*], Christopher J.L. Murray [*]

Seattle, WA, USA; New York, NY, USA; Cape Town, South Africa; and London, UK

BACKGROUND Ischemic heart disease (IHD) is the leading cause of death worldwide. The Global Burden of Diseases, Injuries and Risk Factors (GBD) 2010 Study estimated IHD mortality and disability burden for 21 world regions for the years 1990 to 2010.

METHODS Data sources for GBD IHD epidemiology estimates were mortality surveillance, verbal autopsy, and vital registration data (for IHD mortality) and systematic review of IHD epidemiology literature published from 1980 to 2008 (for nonfatal IHD outcomes). An estimation and validation process led to an ensemble model of IHD mortality by country for all 21 world regions, adjusted for country-level covariates. Disease models were developed for the nonfatal sequelae of IHD: myocardial infarction, stable angina pectoris, and ischemic heart failure.

RESULTS Country-level covariates including metabolic and nutritional risk factors, education, war, and annual income per capita contributed to the ensemble model for the analysis of IHD death. In the acute myocardial infarction model, inclusion of troponin in the diagnostic criteria of studies published after the year 2000 was associated with a 50% higher incidence. Self-reported diagnosis of angina significantly overestimated stable angina prevalence compared with "definite" angina elicited by the Rose angina questionnaire. For 2010, Eastern Europe and Central Asia had the highest rates of IHD death and the Asia Pacific High-Income, East Asia, Latin American Andean, and Sub-Saharan Africa regions had the lowest.

CONCLUSIONS Global and regional IHD epidemiology estimates are needed for estimating the worldwide burden of IHD. Using descriptive meta-analysis tools, the GBD 2010 standardized and pooled international data by adjusting for region-level mortality and risk factor data, as well as study-level diagnostic method. Analyses maximized internal consistency, generalizability, and adjustment for known sources of bias. The GBD IHD analysis, nonetheless, highlights the need for improved IHD epidemiology surveillance in many regions and the need for uniform diagnostic standards.

This research was supported by the Bill and Melinda Gates Foundation and U.S. National Heart, Lung, and Blood Institute award K08 HL089675-01A1 to A.E.M.

From the *Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA; †Division of General Medicine, Department of Medicine, Columbia University Medical Center, New York, NY, USA; ‡Department of Cardiology, University of Washington, Seattle, WA, USA; §Department of Medicine, University of Cape Town, Cape Town, South Africa; ||MRC-HPA Centre for Environment and Health and Department of Epidemiology and Biostatistics, Imperial College London, London, UK. Correspondence: Andrew E. Moran (aem35@columbia.edu).

GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 331-342

Ischemic heart disease (IHD) is the world's leading cause of death [1]. Large-scale IHD treatment and prevention programs require accurate burden of disease assessment at the regional level. The Global Burden of Disease (GBD) Study was commissioned by World Bank in 1991 (GBD 1990) [2,3] as an effort to provide summary measures of mortality and disability/morbidity for 8 world regions using standard measures across diseases, including cardiovascular disease [4,5]. The GBD 2004 estimated burden for IHD and other cardiovascular diseases in 14 regions [6]. Acute myocardial infarction (AMI), stable angina, and heart failure after AMI were estimated separately and then aggregated to calculate total burden of IHD [6].

The GBD 2010 study aimed to estimate the burden of cardiovascular disease in greater detail using more primary data, and new methods were developed for IHD burden estimation. Incidence and prevalence of IHD sequelae were informed primarily by regional IHD death rates. Estimating regional IHD mortality was complicated by the need to reallocate IHD deaths erroneously assigned to ill-defined cardiovascular causes [7]. A systematic review of IHD incidence, prevalence, case-fatality, and mortality studies published from 1980 to 2008 added additional information, but the review also identified analytic challenges: Methods for measuring IHD cases varied between studies, regions, and time periods; and limited published data were available for low- and middle-income regions [8]. GBD 2010 sought to make country-level estimates for the years 1990, 2005, and 2010 and to generate quantitative measures of uncertainty for incidence, prevalence, case-fatality, mortality, and other measures of burden. In this paper, we describe the analytic approach and present global IHD epidemiology estimates for 2010 in 21 world regions (country and region list, Supplemental Table 1).

METHODS

Overview. The epidemiologic components of IHD burden are IHD death and morbidity from AMI, stable angina, and ischemic heart failure [8]. IHD was 1 of 291 GBD major causes of death most often categorized into International Classification of Diseases (ICD)-9 codes 410 to 414 and ICD-10 codes I20 to I25 (Table 1). IHD mortality was analyzed using a standard cause of death ensemble model (CODEm) algorithm [9]. Nonfatal IHD burden was captured by estimating the prevalence of AMI, stable angina, and ischemic heart failure.

Table 1. GBD cause mapping for the *International Classification of Diseases* (*Revision 10, Revision 9,* and *Revision 9-BTL*)

GBD Name	ICD-10	ICD-9	ICD-9-BTL
Ischemic heart disease	I20–I25	410–414	B27

GBD, Global Burden of Diseases Study.

Nonfatal AMI, stable angina, and heart failure envelope data were analyzed using DisMod-MR, a meta-regression Bayesian modeling tool (Disease Model, Meta-Regression, Institute for Health Metrics and Evaluation, Seattle, WA, USA) [10,11]. Prevalence of heart failure and proportion of heart failure of ischemic origin were estimated separately and were used to estimate prevalence of ischemic heart failure.

IHD mortality data. We aggregated cause-specific mortality data in a central database. Mortality data were gathered from vital registration, verbal autopsy, surveillance systems, survey/census, or police reports. Starting with raw cause-of-death data, comparability was enhanced by mapping across various ICD versions (Table 1). We enhanced verbal autopsy data by different methods and used these in the analysis with other sources of data [12–17]. Table 2 shows the number of data points by type of source (vital registration, verbal autopsy, and surveillance system) and by decade.

A key element of the analysis of cause-of-death data was to take the raw cause-of-death data and enhance comparability by mapping across various revisions and national variants of the ICD and to process garbage codes [7,18]. Garbage codes are the deaths that have been coded to an intermediate, immediate, or ill-defined cause and must instead be attributed to the underlying causes. Supplemental Table 2 presents total increase and percent increase by each garbage code as well as proportion of each garbage code assigned to IHD in our ICD-10 data. Overall IHD death was increased about 21.5% after redistribution. Half of this increase originated from reallocation of deaths coded to senility (ICD-10 R54), hypertension (I10), atherosclerosis (I70), and all cardiac conduction disorders

Table 2. Site-years by decade and source type of IHD mortality data

Source Type	1980–1989	1990–1999	2000–2011
Surveillance	0	27	24
Verbal autopsy	14	14	42
Vital registration	802	957	945

IHD, ischemic heart disease.

to IHD (I44,I45). About 77% of heart failure deaths were assigned to IHD death globally (Supplemental Table 2). Deaths coded to heart failure—an intermediate cause of death under ICD rules—were redistributed to 17 causes including IHD [19]. The proportion of deaths originally coded as heart failure and moved to IHD was estimated by modeling the etiologies of heart failure [19]. Detailed methods for garbage code redistribution have been published elsewhere [7].

IHD cause of death model covariates. Several covariates were used as candidate covariates to inform estimation for the country-years without data. The units of analysis were country, year, age, and sex. Covariates were chosen based on a significant association with IHD death at the individual level and an expected effect at the ecological level (Table 3). The assumed direction of effect was based on disease pathophysiology and the possible effect of the covariate at individual and population level derived from the past literature. A separate arm of the GBD 2010 estimated the level of covariates for each country separately. Based on the nature and sources of data, different sources such as country surveys, censuses, international organizations such as different U.N. agencies were analyzed. Different methods were employed for this estimation [19–22]. These separate reviews also catalogued published association of risk factors such as Omega-3 fatty acid consumption, cholesterol, and systolic blood pressure with IHD [23].

Covariates were divided into 3 groups based on strength of epidemiological evidence and presumed proximity to IHD in the chain of causation. Level 1 covariates were those for which there was strong evidence of a biologically plausible association with IHD: diabetes mellitus prevalence, smoking and cigarette consumption, and mean body mass index, serum cholesterol, and systolic blood pressure (Supplemental Table 3). Level 2 covariates included

Table 3. Country-level covariates, acceptable direction of effect, number of models, and final contribution in estimating IHD mortality in ensemble method

		Men			Women		
Covariate	Level	CF*	Rate	Contribution	CF*	Rate	Contribution
Cumulative cigarette consumption, mean 5-year per capita cigarette consumption [48]	1	89	139	30%	113	82	49%
Diabetes prevalence [46]	1	47	0	30%	0	0	0%
Mean body mass index, kg/m^2 [49]	1	73	0	35%	114	0	42%
Mean systolic blood pressure, mm Hg	1	50	82	25%	108	64	58%
Mean serum cholesterol, mmol/l	1	47	57	55%	114	43	67%
Prevalence of smoking, self-reported active smoking status [48]	1	87	120	61%	104	71	49%
Alcohol consumption, liters per capita [50]	2	74	122	11%	110	80	42%
Animal fat consumption, kcal per capita	2	62	106	10%	0	0	0%
Health system access, unitless	2	0	46	0%	19	42	4%
Fruit consumption, kcal per capita [51]	2	0	109	0%	0	77	0%
PUFA3 consumption, kcal per capita	2	90	84	18%	81	74	32%
Vegetables consumption, kcal per capita [51]	2	30	102	16%	0	64	0%
Milk consumption, kcal per capita [52]	2	0	128	0%	13	106	7%
Nut and seed consumption, kcal per capita [53]	2	19	101	0%	0	58	0%
Disaster death, rate per 1,000 person-years [54]	3	0	0	0%	10	0	3%
Education, years per capita [34,37]	3	0	41	0%	63	15	30%
Lag country income, US$ per capita [34,37]	3	16	53	10%	57	20	25%
PUFA6 consumption, kcal per capita	3	0	20	0%	0	23	0%
Population elevation, % of population dwelling at >1,500 m [55]	3	67	65	22%	84	51	34%
Legume and pulses consumption, kcal per capita [56]	3	27	64	0%	37	35	12%
Red meat consumption, kcal per capita [57,58]	3	31	66	6%	24	27	5%
War death, rate per 1,000 person-years [59]	3	0	70	0%	37	70	18%
Whole grain consumption, kcal per capita	3	0	0	0%	0	0	0%

IHD, ischemic heart disease; PUFA, polyunsaturated fatty acid.
* Logit of cause fraction (CF) expressed as a dependent variable in the model.

GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 331-342

covariates with some evidence of association but with an indirect causal relationship, such as health system access and alcohol, animal fat, polyunsaturated fatty acid (PUFA) 3, fruits, vegetables, milk, and nut consumption. Evidence for level 3 covariates was observed in time-series or cross-sectional studies: PUFA 6, legumes, red meat, and whole grain consumption and country income per capita, education, disaster, elevation, and war.

Two main families of IHD mortality models were tested in the analysis: rate models (logarithm of rate as dependent variable) and cause fraction models [logit of cause fraction: $\ln(cf/1-cf)$]. In the first step, a mixed-effect regression for all possible combinations of level 1 covariates was estimated (with different number of covariates). All models for which the direction was plausible and the coefficient association was significant at the p value <0.05 level were retained. Level 2 and 3 covariates were added to these models using a forward technique checking all order-independent combinations. All covariates had an a priori defined direction of effect on IHD except alcohol consumption (both negative and positive coefficients would be acceptable) [24,25]. The number of times a covariate was "picked up" by the covariate selection process was the indicator of independent ecological association between the covariate and IHD death. We calculated and presented a final contribution index for all covariates by counting the number of times each covariate was presented in the models contributed in final estimation by providing at least 1 of 1,000 draws.

Mortality analysis, CODEm model. CODEm explores a large variety of possible models to estimate trends in causes of death. Possible models are identified using a covariate selection algorithm that yields many plausible combinations of covariates that are then run through 4 model classes. The model classes include mixed-effects linear models and spatiotemporal Gaussian process regression models for cause fractions and death rates. All models for each cause of death are then assessed using out-of-sample predictive validity and combined into an ensemble with optimal out-of-sample predictive performance. Absolute median relative error is the overall index of model validity and is calculated by comparing the model prediction with observed point of data. The ensemble model produces uncertainty intervals for each age-country-year for mortality. The 1,000 draws from the Gaussian process regression step provided uncertainty intervals to generate distributions of mortality in all age-country-year groups.

IHD out-of-sample predictive validity of component models. The ensemble modeling strategy assessed the performance of various component models. We formally evaluated the ability of each of these models to make accurate predictions by creating 20 train-test-test splits. For each of these datasets, we randomly assign 70% of the data to the train set, 15% to the first test dataset, and the last 15% to the second test dataset. For each train dataset, we re-estimated each of the proposed models including both the mixed-effects and the spatial-temporal models. The test data were not included in the model estimation; therefore, the performance of each model was evaluated out-of-sample. Out-of-sample predictions for the test set are a fair evaluation of how each model will perform in predicting IHD mortality where the data are sparse or missing.

Predictive validity was evaluated using 3 metrics. First, we evaluated how well each model predicted age-specific death rates using the root mean squared error (RMSE) of the log of the death rate. Second, we also wanted models that predict accurate trends. To achieve this, for the test data, we computed the log death rate in year t minus the log death rate in year t-1. We also computed similar metric for the prediction. We then counted the percentage of the time that the model predicts the same trend as the test data and proportion of the data in the test set included in the 95% prediction interval of the component model estimation. The prediction interval was based both on the uncertainty in the predicted death rate due to the models and the data variance for each observation.

IHD corrected cause fractions based on the mortality envelope (CODCorrect process). In order to take advantage of using all cardiovascular death data and to produce a more accurate estimate of IHD deaths over time, we modeled death at different cause levels. Different levels of analysis for cardiovascular diseases were presented in Box 1. We corrected all cardiovascular mortality such that the sum of all cause-specific deaths equals the all-cause mortality "envelope." In addition, mortality rate estimations from cardiovascular causes (rheumatic heart disease, IHD, cerebrovascular disease, and other cardiovascular diseases) were rescaled so that sum of deaths equals all-cardiovascular death.

Estimating morbidity of IHD. Nonfatal IHD sequelae prevalence and incidence were estimated

BOX 1. Different levels of causes of death (related to cardiovascular causes) applied in CODCorrect process in Global Burden of Diseases Study 2010.

Level 1: All-cause mortality (envelope)
Level 2: B.2. Cardiovascular and circulatory diseases
Level 3: B.2.1. Rheumatic heart disease
Level 3: B.2.2. Ischemic heart disease
Level 3: B.2.3. Cerebrovascular disease
Level 4: B.2.3.1. Ischemic stroke
Level 4: B.2.3.2. Hemorrhagic and other nonischemic stroke
Level 3: B.2.4. Hypertensive heart disease
Level 3: B.2.5. Cardiomyopathy and myocarditis
Level 3: B.2.6. Atrial fibrillation and flutter
Level 3: B.2.7. Aortic aneurysm
Level 3: B.2.8. Peripheral vascular disease
Level 3: B.2.9. Endocarditis
Level 3: B.2.10. Other cardiovascular and circulatory diseases

using DisMod-MR software. DisMod-MR is a meta-regression mathematical modeling tool for modeling epidemiological measures of a disease together. In a Bayesian approach, first, uses all parameters (prevalence, incidence, and case fatality) in a grand model considering country, region, and super-region effects to come up with a rough estimate for each region, year, sex, and age. It uses different study-level covariates (to represent study differences such as diagnostic method or source of data), and country-level covariates (such as health system performance and standardized stroke mortality rate). The first step estimates are called empirical priors. In the second step, the empirical prior is updated with local data (region, year, sex, and age) to produce posterior distribution of each parameter. The core mathematical model of DisMod-MR is based on a compartmental model including susceptible population, patients, death, in addition to the rate of transition. A comprehensive explanation for DisMod-MR has been published in an appendix [19] to GBD capstone papers in the *Lancet* and in a separate paper [10]. Specific modeling strategies and assumptions applied in DisMod-MR modeling were summarized in Supplemental Box 1.

AMI model. DisMod-MR [10,11,19] was used to estimate the total number of patients living with AMI. An AMI was assumed to cause symptoms up to 28 days. The standard time frame for case fatality was 28 days because it was the interval defined by the MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) study (the highest quality case fatality data with the most years covered), but 30-day case fatality data were also analyzed. Because of the limitations of population-based survey measures of old MI prevalence (i.e., self-report of prior MI or Q waves on resting electrocardiogram) [8], 2 types of data were used in the AMI model: AMI incidence; and AMI 28-day case fatality. For papers identified in a systematic review of IHD epidemiology, data on AMI epidemiology, years of observation, nation or region, age, sex, diagnostic definition, and use of troponin enzyme in AMI diagnosis were abstracted [8]. The GBD definition of AMI was based on the 2007 World Health Organization (WHO) diagnostic definition [8,26]. Detection of positive troponin, a biomarker of myocardial injury, is a key component of the WHO category A definition, but troponin measures were not commonly used for AMI diagnosis in high-income studies until around the year 2000. To this day, troponins are still not widely used in many low- and middle-income regions. Therefore, the WHO 2007 category B AMI definition—including cases lacking cardiac biomarker measurement—was also employed. In the analysis, a study-level variable categorized AMI incidence data as reporting of troponin measurement or not and assumed all studies published prior to 2000 did not measure troponin.

Twenty-eight–day case fatality was converted to a rate (hazard) by the formula:

$$\textit{excess mortality rate} = \frac{-\ln(1 - 28 \text{ day case fatality})}{(28/365)}$$

IHD age-standardized death rate was used as a country-level covariate in DisMod-MR to inform prevalence multiplied by excess mortality. This allowed DisMod-MR to adjust the level of incidence and excess mortality according to regional MI mortality. We estimated proportion of MI mortality in IHD mortality, MI/IHD mortality ratio, at the region, age, and sex level from the cause of death database (vital registration data with ICD-9 and ICD-10 codes in detail). The ratio of MI/IHD mortality was applied to IHD death to estimate MI mortality rate in DisMod-MR. The MI/IHD mortality ratio was particularly low in Eastern Europe and was particularly high in the Sub-Saharan Africa regions (Supplemental Box 2). Because we used the IHD death rate as a country-level covariate, we did

GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 331-342

not use the additional covariates that were included in the production of these death rates during the CODEm process (i.e., smoking, mean serum cholesterol, systolic blood pressure, nutritional factors, income, and health system access).

Angina pectoris. Most of the studies of angina pectoris included from the GBD systematic review were population-based surveys that assessed angina prevalence using the Rose angina questionnaire, self-reported physician's diagnosis of angina, or more rarely physician-reported diagnosis or self-reported use of antianginal medications [8]. We found at least 1 point of prevalence data for 90 countries and 18 GBD regions. Incidence data were found only for the United States, Finland, and South Africa. We also used case-fatality data in terms of standardized mortality ratio and relative risk of mortality from angina natural history studies to inform the model estimation [8]. Study-level variables categorized method of diagnosing angina; Rose questionnaire definite angina was set as the standard method. Prevalence of stable angina from 2 surveys—the WHS (World Health Study) and MEPS (Medical Expenditure Panel Survey) [27]—were used to informed age distribution and level of stable angina in regions. Separate variables categorized estimates based on the diagnostic definition: Rose "definite" angina (our standard definition); reporting Rose "probable" angina; or self-reported history of angina. For DisMod-MR, IHD mortality rate was used as a country-level covariate, precluding use of covariates used in cause-of-death estimation.

Ischemic heart failure. The first step toward estimating the burden of ischemic heart failure was to estimate the total heart failure envelope. Data were derived from the IHD systematic review or from hospital discharge data for 24 countries [8]. For the hospital discharge data, the U.S. State Inpatient Database was used to calculate a correction factor for heart failure using uniquely identifiable individuals. This correction factor adjusted for the fact that 1 person may be hospitalized in multiple admissions in the database. To calculate the correction factor, we tallied the number of all patient records with heart failure and divided it by the number of unique patients in the dataset by age and sex. We then applied this correction factor to the other hospital datasets without patient identifiers by extracting all heart failure records and dividing by the correction factor. The correction factor values ranged from 1.12 to 1.76 depending on patient age and sex.

Because some prevalence and case-fatality data were reported for more severe cases (≥New York Heart Association class III), we defined a study level covariate to adjust for severity. We included age-standardized death rate due to cardiomyopathy (ICD-9 425 or ICD-10 I42) as a country-level covariate. Average body mass index (over age 20 years) was included based on review of the literature [28]. We did not include other risk factors for heart failure such as hypertension and smoking because their direction was not plausible in DisMod-MR models (Supplemental Box 1).

Once the heart failure envelope was estimated, the second step was to estimate the proportion of heart failure cases attributable to IHD [29]. The distribution of 7 major heart failure causes identified among heart failure patients was estimated from the systematic review and hospital records at the individual level from the United States, Canada, Brazil, and Mexico: IHD; hypertensive heart disease; Chagas disease; non-Chagas cardiomyopathies; cardiopulmonary disease; valvular heart disease; and category of other remaining etiologies. To produce the etiologic fraction for the major etiology groups, we applied a hierarchical model using super-region, region, and country random effects on the proportion of heart failure by DisMod-MR. Country-level covariates, when applicable, informed prediction for countries without data. By applying the etiologic fraction for each cause to the heart failure prevalence on an age- and region-specific basis, the prevalence of ischemic heart failure was estimated [19].

Statistics. Uncertainty intervals were reported based on 2.5 and 97.5 percentiles of the posterior distribution of the parameter in 1,000 draws followed through different steps of the analysis but were not reported here. The p values of the ensemble model were estimated in a 1- or 2-sided basis if the posterior distribution includes the null difference or zero difference. Incidence and mortality rates and prevalence proportions were age standardized using the direct method and the WHO reference population [30]. Results for 2010 were reported by GBD region; countries composing each region are listed in Supplemental Table 1.

RESULTS

IHD mortality. Smoking indicators, cholesterol, and mean systolic blood pressure contributed significantly to the IHD mortality model (Table 3). Alcohol was selected most often from level 2, perhaps because either direction of effect was

accepted. Among level 2 covariates, animal fat, fruit, and vegetable consumption were picked up more often than PUFA 3 consumption. But in terms of informing final estimation, PUFA 3 and vegetable consumption contributed more significantly than other level 2 covariates. Health system access was picked up moderately. All nutritional and socioeconomic factors were significantly correlated with IHD death. Body mass index and diabetes prevalence from level 1 and disaster deaths and whole grain consumption from level 3 were not significantly correlated with IHD death.

In final IHD mortality ensemble estimate, body mass index, systolic blood pressure, cholesterol, and smoking contributed significantly. Contextual covariates such as country income, education, and war also contributed substantially to the IHD death ensemble model, especially in women. Overall, only cause fraction models (linear and space-time models) were selected by out-of-sample, external validity criteria for final estimation. Rate models did not have comparable external validity.

In total, there were 164 cause fraction models selected for men and 210 for women. In addition, there were 232 rate models selected for men and 141 for women. The final ensemble models selected for men and women performed well in terms of RMSE of the log of the death rate, proportion with correct trend, and percent of data covered by the model's 95% confidence interval (CI) (Supplemental Table 4). The average out-of-sample RMSE was lower (0.65 for women and 0.58 for men) in the ensemble model compared with the best individual model (0.66 for women and 0.59 for men). In addition, the data coverage in the ensemble model was superior. Estimated deaths due to IHD and other individual causes were rescaled to the total mortality envelope. Supplemental Figure 1 illustrates deaths due to IHD and other individual causes before and after this process (CODCorrect step).

IHD death rate was age standardized for ages ≥30 years and all GBD regions for 2010 (Table 4). IHD death rate was highest in Eastern Europe and Central Asia. Following these, Central Europe and North Africa, Middle East regions had the highest rates of IHD death. The 4 Sub-Saharan Africa regions, Latin America Andean, and East Asia had among the lowest IHD death rates.

MI incidence. After adjusting for IHD mortality rate as well as super-region and region effects, there was not considerable heterogeneity between countries in each region (Supplemental Fig. 2).

Table 4. Age-standardized IHD mortality rate per 1,000 persons, age ≥30 years, 2010

Region	Women	Men	Total
Asia Pacific, High Income	0.5	0.8	0.6
Asia, Central	3.9	6.9	5.2
Asia, East	0.9	1.4	1.2
Asia, South	1.8	2.9	2.3
Asia, Southeast	1.1	1.9	1.5
Australasia	1.1	1.6	1.4
Caribbean	1.9	2.5	2.2
Europe, Central	2.0	3.5	2.7
Europe, Eastern	4.3	7.7	5.7
Europe, Western	1.0	1.7	1.3
Latin America, Andean	0.9	1.2	1.0
Latin America, Central	1.3	2.0	1.6
Latin America, Southern	1.1	1.9	1.5
Latin America, Tropical	1.3	2.0	1.7
North Africa/Middle East	2.0	3.1	2.5
North America, High Income	1.5	2.2	1.8
Oceania	1.6	2.1	1.9
Sub-Saharan Africa, Central	1.4	1.9	1.6
Sub-Saharan Africa, East	0.8	1.0	0.9
Sub-Saharan Africa, Southern	0.8	1.3	1.0
Sub-Saharan Africa, West	1.0	1.0	1.0

IHD, ischemic heart disease.

IHD mortality was a positive and significant covariate (p value <0.005). Incidence of MI was overall about 2.0 (95% CI: 1.85 to 2.26) times higher in men than in women. Analysis of covariate coefficients suggested that estimated AMI incidence is 51% (95% CI: 46% to 56%) lower when positive troponin was not used to diagnose AMI. Incidence was 13% lower (95% CI: 5% to 20%) when only non-fatal MI was reported and 26% lower (95% CI: 16% to 34%) when only first-ever MI was reported (differences significant at 0.001 level). The DisMod-MR model output for Western Europe demonstrates how closely the final estimate follows the data (adjusted for study level covariates) (Online Fig. 3). In general, AMI incidence in 2010 had a regional distribution similar to IHD death, though AMI incidence estimated for Sub-Saharan Africa was no longer among the lowest (Table 5). There was a smaller ratio of MI incidence to IHD death in Asia Pacific High Income compared with higher IHD risk regions such as Eastern Europe, Central Asia, and North Africa, Middle East. The implication is that patients die of AMI in high IHD mortality rate countries and more patients die due to the chronic sequelae of IHD in low IHD mortality regions such as Asia Pacific High Income.

In a preliminary model, AMI 28-day case fatality was higher in high IHD mortality regions and

GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 331-342

Table 5. Age-standardized incidence of MI per 1,000 persons, age ≥30 years, 2010

Region	Women	Men	Total
Asia Pacific, High Income	1.08	2.21	1.61
Asia, Central	4.09	7.12	5.40
Asia, East	1.63	2.73	2.17
Asia, South	3.10	4.96	4.01
Asia, Southeast	2.16	3.54	2.80
Australasia	1.94	3.79	2.83
Caribbean	2.96	4.27	3.58
Europe, Central	2.91	5.45	4.04
Europe, Eastern	4.12	8.29	5.79
Europe, Western	1.84	3.90	2.81
Latin America, Andean	2.11	3.06	2.56
Latin America, Central	2.60	4.05	3.28
Latin America, Southern	1.96	3.97	2.86
Latin America, Tropical	2.45	4.20	3.25
North Africa/Middle East	3.43	5.35	4.36
North America, High Income	2.05	3.91	2.91
Oceania	2.55	3.96	3.20
Sub-Saharan Africa, Central	3.29	4.46	3.83
Sub-Saharan Africa, East	2.83	3.50	3.14
Sub-Saharan Africa, Southern	2.40	3.54	2.89
Sub-Saharan Africa, West	3.02	3.61	3.30

MI, myocardial infarction.

Table 6. Twenty-eight–day case-fatality proportion of MI in age ≥45 years, 2010

Region	Women	Men
Asia Pacific, High Income	0.27	0.29
Asia, Central	0.64	0.75
Asia, East	0.44	0.42
Asia, South	0.51	0.52
Asia, Southeast	0.42	0.46
Australasia	0.34	0.36
Caribbean	0.51	0.52
Europe, Central	0.51	0.59
Europe, Eastern	0.63	0.73
Europe, Western	0.35	0.39
Latin America, Andean	0.38	0.39
Latin America, Central	0.46	0.49
Latin America, Southern	0.38	0.44
Latin America, Tropical	0.47	0.48
North Africa/Middle East	0.54	0.54
North America, High Income	0.37	0.39
Oceania	0.51	0.53
Sub-Saharan Africa, Central	0.55	0.57
Sub-Saharan Africa, East	0.46	0.43
Sub-Saharan Africa, Southern	0.42	0.45
Sub-Saharan Africa, West	0.51	0.46

MI, myocardial infarction.

higher in women than in men (Supplemental Fig. 4). But, after adjusting for IHD mortality rate, 28-day case fatality was slightly higher in men than in women (Table 6).

Angina prevalence. Overall, Rose definite stable angina was more prevalent in men than in women (1.13, 95% CI: 1.04 to 1.22) (Table 7, Supplemental Fig. 5). Other case definitions led to prevalence estimates higher than the main estimate: "probable" angina by Rose questionnaire or using other questionnaires: 12% higher (95% CI: 7% to 34%); self-report of stable angina diagnosis: 78% higher (95% CI: 64% to 94%); and diagnosis reported by the study physician: 37% higher (95% CI: 25% to 52%). Prevalence of angina was significantly correlated with the IHD standardized death rate. WHS estimates for Sub-Saharan Africa nations were very close to the main prevalence estimate for Sub-Saharan Africa regions (relative prevalence: 0.96, not significant at 0.05). WHS country survey estimates were 21% higher than the main regional prevalence estimates in other regions (relative prevalence: 1.21; p value = 0.05). Because of sparse data on stable angina incidence, coefficients for predictors of angina incidence were unstable except for a significant correlation with IHD standardized death rate (p value = 0.02).

Eastern Europe and Central Asia had the highest angina prevalence in 2010 (Supplemental Fig. 6). For most regions, angina prevalence in

Table 7. Age-standardized prevalence proportion of stable angina per 100 persons, age ≥30 years, 2010

Region	Women	Men	Total
Asia Pacific, High Income	2.5	3.3	2.9
Asia, Central	5.0	6.8	5.8
Asia, East	3.0	3.7	3.3
Asia, South	2.5	3.2	2.8
Asia, Southeast	2.6	3.3	3.0
Australasia	2.8	3.6	3.2
Caribbean	2.8	3.4	3.1
Europe, Central	3.3	4.5	3.8
Europe, Eastern	4.7	6.6	5.4
Europe, Western	2.8	3.8	3.2
Latin America, Andean	2.4	2.9	2.7
Latin America, Central	2.7	3.4	3.0
Latin America, Southern	2.3	3.3	2.8
Latin America, Tropical	4.0	5.1	4.5
North Africa/Middle East	3.7	4.6	4.1
North America, High Income	2.5	3.3	2.9
Oceania	2.8	4.1	3.4
Sub-Saharan Africa, Central	2.5	3.4	2.9
Sub-Saharan Africa, East	3.2	3.9	3.5
Sub-Saharan Africa, Southern	2.7	3.5	3.1
Sub-Saharan Africa, West	3.3	3.8	3.5

middle age (ages 20 to 40 years) was less than 4%. Prevalence was estimated to decrease after age 80 years as incidence decreases, whereas excess mortality still increased. Incidence of stable angina was estimated to be more than 3 cases per 1,000 in Eastern Europe and Central Asia (Table 8).

Ischemic heart failure prevalence. The proportion of the total heart failure prevalence envelope attributed to IHD was the highest in developed countries besides Latin America and North Africa/Middle East; this fraction was the smallest in Sub-Saharan Africa (Supplemental Fig. 7). Table 9 lists estimated prevalence of IHD heart failure by region in 2010.

DISCUSSION

IHD is a leading cause of death and disability worldwide and estimating IHD epidemiology as accurately as possible for all world regions is of crucial importance. The GBD 2010 study combined different sources of data and definitions in order to estimate numbers of IHD deaths, AMI incidence, and prevalence of stable angina and ischemic heart failure for 21 world regions for the years 1990 and 2010. For IHD mortality, we demonstrated that an ensemble method approach improved the external validity of results, captured local differences between countries, and revealed hidden temporal trends by country. A novel software program, DisMod-MR, was used to estimate prevalence and incidence of AMI, angina, and ischemic heart failure.

The backbone of nonfatal IHD burden estimation was IHD death rates, estimated from regional source data after reallocation of "garbage coded" cardiovascular deaths to IHD. We employed current knowledge on metabolic and nonmetabolic factors to inform estimation for many countries where no hard evidence was available. Out-of-sample predictive validity confirmed the generalizability of the results and demonstrated that an ensemble method of regional IHD mortality rates provides a more stable approach that minimizes the effects of outlying data and improves the external validity of the results. Country-level covariates contributed in ensemble model were consistent with the IHD risk factor literature [31]. The association we found between education, income, and IHD death has been observed in other studies [32–37]. Associations between risk factors and IHD were ecological and the strength of the associations may not be equal to what would be observed at the level of the individual for risk factors such as smoking, cholesterol, and blood pressure [38]. However, estimating the association between

Table 8. Age-standardized incidence rate of stable angina pectoris per 1,000 persons, age ≥30 years, 2010

Region	Women	Men	Total
Asia Pacific, High Income	2.26	2.87	2.56
Asia, Central	4.56	6.39	5.37
Asia, East	2.53	3.15	2.84
Asia, South	2.74	3.57	3.16
Asia, Southeast	2.26	2.85	2.54
Australasia	2.42	3.11	2.76
Caribbean	2.50	3.14	2.80
Europe, Central	2.99	4.01	3.46
Europe, Eastern	3.84	5.54	4.54
Europe, Western	2.28	3.06	2.65
Latin America, Andean	2.22	2.58	2.39
Latin America, Central	2.41	2.96	2.67
Latin America, Southern	2.11	3.02	2.53
Latin America, Tropical	3.12	4.08	3.57
North Africa/Middle East	3.40	4.27	3.83
North America, High Income	2.45	3.35	2.88
Oceania	2.48	3.88	3.15
Sub-Saharan Africa, Central	2.22	3.10	2.63
Sub-Saharan Africa, East	2.66	3.21	2.92
Sub-Saharan Africa, Southern	2.33	2.95	2.61
Sub-Saharan Africa, West	2.80	3.18	2.98

Table 9. Age-standardized prevalence proportion of ischemic heart failure per 100 persons, age ≥30 years, 2010

Region	Women	Men	Total
Asia Pacific, High Income	0.18	0.29	0.23
Asia, Central	0.38	0.68	0.51
Asia, East	0.17	0.23	0.20
Asia, South	0.26	0.37	0.32
Asia, Southeast	0.29	0.34	0.31
Australasia	0.34	0.65	0.49
Caribbean	0.37	0.43	0.40
Europe, Central	0.44	0.61	0.52
Europe, Eastern	0.54	1.10	0.75
Europe, Western	0.47	0.84	0.64
Latin America, Andean	0.23	0.23	0.23
Latin America, Central	0.27	0.33	0.30
Latin America, Southern	0.52	0.77	0.63
Latin America, Tropical	0.33	0.41	0.37
North Africa/Middle East	0.64	0.58	0.61
North America, High Income	0.79	1.17	0.97
Oceania	0.90	1.03	0.96
Sub-Saharan Africa, Central	0.16	0.24	0.19
Sub-Saharan Africa, East	0.16	0.28	0.22
Sub-Saharan Africa, Southern	0.35	0.38	0.36
Sub-Saharan Africa, West	0.11	0.15	0.13

GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 331-342

protective factors or risk factors and IHD at the country and single-year level is important for policy making at the population level and may generate hypotheses for individual level research [38]. Because of the unpredictable nature of some risk factors such as country income, disaster, and war, the most feasible approach to studying their hazardous effect may be through ecological and time series studies [38]. Evidence of independent effects of contextual covariates such as education, war, and income lends support to the hypothesis that IHD originates not only from individual behavior, but also at the societal level [39].

In recent years, a new "universal" definition of AMI was promoted, advocating for diagnosis based on a troponin biomarker level at least 1 value above the 99th percentile of the upper reference limit in addition to classic clinical symptoms and signs [40]. A study-level "troponin use" variable addressed the challenge of MI incidence data that did not incorporate troponin measures over time (troponins were not widely available until after about 1995) or space (troponin testing is unavailable even today in many regions). Troponin improves sensitivity without sacrificing specificity of MI [41,42]. Previous studies reported that troponin improves the under detection of MI cases by approximately 40% to 70% [43]. Though not restricted to comparing studies adhering strictly to the "old" and "new" WHO AMI diagnostic definitions [44], our estimate suggests that almost one-half of all AMI cases are not detected when troponins are not used for diagnosis. All future studies estimating AMI incidence trends will need to adjust for temporal and regional differences in the use of troponins use and other important diagnostic methods.

The analysis of stable angina prevalence adjusted for use of different instruments, definitions, and information sources. We found that on average, studies reporting self-report of angina history (specifically, positive response to the question "Has a doctor told you of a diagnosis of angina?") led to prevalence estimates that were 78% higher (95% CI: 64% to 94%) than prevalence estimated using Rose questionnaire definite angina. This difference could be due to physicians having access to more historical information or poor sensitivity on the part of the Rose questionnaire. It is unknown whether cardiac stress testing with or without coronary perfusion scanning increases or decreases the rate of angina diagnosis, or even if these tests are the appropriate gold standard for comparison with survey questionnaire-based angina diagnosis [45]. Lacking a gold standard for determining which instrument had more accuracy and reliability across populations, we chose Rose definite angina over self-reported history as the standard because it was the conservative choice and because the Rose questionnaire was used in the WHS, leading to better global coverage.

The strengths of this analysis were that it was based on comprehensive cause-of-death data covering all 21 regions and every year from 1990 to 2010, study-level data from a large and validated systematic review of the worldwide IHD epidemiology literature, and methods for achieving an internally consistent disease model of IHD, estimating missing data, and adjusting measurable sources of bias. The GBD IHD estimation also had limitations. Primarily, methods developed for estimating missing data and adjusting for measurement differences among source studies are no real substitute for high-quality IHD surveillance data from every GBD region, using standardized case definitions and measurement methods. IHD risk factors are well known at the individual level. For the ecological and country levels, the effect may not be identical to those effects at the individual level, which may produce difficulties in interpretation. Some factors such as diabetes prevalence and fasting blood glucose are known to be important at the individual level [46], but for modeling at the country level, these covariates showed minor effects. We did not count the quality-of-life or mortality impact of invasive procedures such as percutaneous coronary interventions or coronary artery bypass graft surgery, nor did we count disability related to unstable angina; most likely, this leads to burden underestimation in high-income regions. The GBD is not designed to ensure that risk factor exposures precede disease outcomes, nor can past data be relied on to predict future trends. For example, the current covariates poorly explain the situation in Sub-Saharan Africa where we estimated that IHD mortality continues to be relatively rare, whereas prevalence of risk factors such as hypertension has been rising [47].

CONCLUSIONS

Health policy and research allocation decisions must be made now, and global burden of disease estimates are an important source of information for decision makers. The GBD 2010 study aimed to provide new IHD burden estimates for 2010 and to improve on past estimates for 1990 by harnessing state-of-the-art methods for analyzing the best available mortality and morbidity data, ensuring disease model internal consistency, and adjusting for measurement bias. We found that IHD

mortality and morbidity in Western, high-income regions was lower in 2010 than in the prior 2 decades, but it remains high in Eastern Europe, Central Asia, North Africa, and the Middle East. IHD appears to have remained relatively less prevalent in the East Asian and Sub-Saharan Africa regions. IHD estimates are still limited by sparse data in many low- and middle-income regions and inconsistent measurement methods among studies and regions. The mission of the GBD IHD expert group was not only to provide estimates of IHD burden worldwide, but also to present the state of current knowledge of global cardiovascular disease epidemiology, and promote improved IHD surveillance worldwide.

ACKNOWLEDGMENTS

The authors sincerely thank the many study participants and investigators of the studies contributing data to this analysis.

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.gheart.2012.10.003

REFERENCES

1. Mendis S, Puska P, Norrving B. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva, Switzerland: World Health Organization; Originally published in 2004. Available at: http://www.who.int/cardiovascular_diseases/resources/atlas/en/. Accessed November 6, 2012.
2. Murray CJ, Lopez AD. Evidence-based health policy—lessons from the Global Burden of Disease Study. Science 1996;274:740–3.
3. Bank World. World Development Report 1993. Investing in Health: World Development Indicators. New York, NY: Oxford University Press; 1993.
4. Lopez AD. Global Burden of Disease and Risk Factors. Washington, DC: World Bank Publications; 2006.
5. Murray CJ, Salomon JA, Mathers CD, Lopez AD. Summary Measures of Population Health: Concepts, Ethics, Measurement and Applications. Geneva, Switzerland: World Health Organization; 2002.
6. Mathers C, Fat DM, Organization WH, Boerma JT. The Global Burden of Disease: 2004 Update. Geneva, Switzerland: World Health Organization; 2008.
7. Global Burden of Disease 2010 Causes of Death Collaborating Group. Global and regional mortality from 235 causes of death for 20 age-groups in 1990 and 2010: a systematic analysis. Lancet. In press.
8. Moran AE, Oliver J, Mirzaie M, et al. Assessing the global burden of ischemic heart disease, part one: methods for a systematic review of the global epidemiology of ischemic heart disease in 1990 and 2010. Global Heart 2012;7:315–29.
9. Foreman K, Lozano R, Lopez A, Murray C. Modeling causes of death: an integrated approach using CODEm. Popul Health Metr 2012;10:1.
10. Flaxman A, Vos T, Murray CJL. The Metaregression of Descriptive Epidemiology Model. Submitted.
11. Barendregt JJ, Van Oortmarssen GJ, Vos T, Murray CJ. A generic model for the assessment of disease epidemiology: the computational basis of DisMod II. Popul Health Metr 2003;1:4.
12. Lozano R, Lopez AD, Atkinson C, et al. Performance of physician-certified verbal autopsies: multisite validation study using clinical diagnostic gold standards. Popul Health Metr 2011;9:32.
13. James SL, Flaxman AD, Murray CJ, Population Health Metrics Research Consortium. Performance of the Tariff Method: validation of a simple additive algorithm for analysis of verbal autopsies. Popul Health Metr 2011;9:31.
14. Murray CJ, Lopez AD, Black R, et al. Population Health Metrics Research Consortium gold standard verbal autopsy validation study: design, implementation, and development of analysis datasets. Popul Health Metr 2011;9:27.
15. Lozano R, Wang H, Foreman KJ, et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet 2011;378:1139–65.
16. Lopez AD, Lozano R, Murray CJL, Shibuya K, editors. Verbal autopsy: innovations, applications, opportunities—improving cause of death measurement. Population Health Metrics article collection. July 27, 2011. Available at: http://www.pophealthmetrics.com/series/verbal_autopsy. Accessed November 6, 2012.
17. Naghavi M, Makela S, Foreman K, O'Brien J, Pourmalek F, Lozano R. Algorithms for enhancing public health utility of national causes-of-death data. Popul Health Metr 2010;8:9.
18. Vos T, Flaxman AD, Naghavi M, et al. The Global Burden of Non-Fatal Health Outcomes for 1,160 Sequelae of 291 Diseases and Injuries 1990—2010: a systematic analysis. Submitted.
19. James SL, Gubbins P, Murray CJ, Gakidou E. Developing a comprehensive time series of GDP per capita for 210 countries from 1950 to 2015. Popul Health Metr 2012;10:12.
20. Gakidou E, Cowling K, Lozano R, Murray CJ. Increased educational attainment and its effect on child mortality in 175 countries between 1970 and 2009: a systematic analysis. Lancet 2010;376:959–74.
21. Finucane MM, Stevens GA, Cowan MJ, et al, Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011;377:557–67.
22. Farzadfar F, Finucane MM, Danaei G, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 2011;377:578–86.
23. Lim SS, Vos T, Flaxman AD, et al. The Burden of Disease and Injury Attributable to 66 Risk Factors in 21

GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 331-342

Regions 1990–2010: a systematic analysis. Lancet. In press.
24. Zaridze D, Brennan P, Boreham J, et al. Alcohol and cause-specific mortality in Russia: a retrospective case-control study of 48,557 adult deaths. Lancet 2009;373:2201–14.
25. Nicholson A, Bobak M, Murphy M, Rose R, Marmot M. Alcohol consumption and increased mortality in Russian men and women: a cohort study based on the mortality of relatives. Bull World Health Organ 2005;83:812–9.
26. Mendis S, Lindholm LH, Mancia G, et al. World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction charts: assessment of cardiovascular risk for prevention and control of cardiovascular disease in low and middle-income countries. J Hypertens 2007;25:1578–82.
27. Agency for Healthcare Research and Quality. MEPS HC-120 2008 Medical Conditions. 2010. Online database. Available at: http://meps.ahrq.gov/data_stats/download_data_files.jsp. Accessed November 6, 2012.
28. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–13.
29. Ahern R, Lozano R, Naghavi M, Foreman K, Gakidou E, Murray CJ. Improving the public health utility of global cardiovascular mortality data: the rise of ischemic heart disease. Popul Health Metr 2011;9:8.
30. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age Standardization of Rates: A New WHO Standard. GPE Discussion Paper Series 31. Geneva, Switzerland: World Health Organization; 2001. Available at: http://www.who.int/healthinfo/paper31.pdf. Last accessed November 13, 2012.
31. Roger VL, Go AS, Lloyd-Jones DM, , et al, for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:e2–220.
32. Blane D, Hart CL, Smith GD, Gillis CR, Hole DJ, Hawthorne VM. Association of cardiovascular disease risk factors with socioeconomic position during childhood and during adulthood. BMJ 1996;313:1434–8.
33. Lynch JW, Kaplan GA, Cohen RD, Tuomilehto J, Salonen JT. Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction? Am J Epidemiol 1996;144:934–42.
34. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation 1993;88:1973–98.
35. Kestilä P, Magnussen CG, Viikari JS, et al. Socioeconomic status, cardiovascular risk factors, and subclinical atherosclerosis in young adults: the cardiovascular risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2012;32:815–21.
36. Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. Stress responsivity and socioeconomic status: a mechanism for increased cardiovascular disease risk? Eur Heart J 2002;23:1757–63.
37. Nordstrom CK, Diez Roux AV, Jackson SA, , et al, for the Cardiovascular Health Study Investigators. The association of personal and neighborhood socioeconomic indicators with subclinical cardiovascular disease in an elderly cohort. The Cardiovascular Health Study. Soc Sci Med 2004;59:2139–47.
38. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
39. Erhardt L, Moller R, Puig J. Comprehensive cardiovascular risk management—what does it mean in practice? Vasc Health Risk Manag 2007;3:587–603.
40. Thygesen K, Alpert JS, White HD, , et al, for the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
41. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. J Am Coll Cardiol 2006;48:1–11.
42. Jaffe AS, Ravkilde J, Roberts R, et al. It's time for a change to a troponin standard. Circulation 2000;102:1216–20.
43. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003;108:2543–9.
44. Salomaa V, Koukkunen H, Ketonen M, et al. A new definition for myocardial infarction: what difference does it make? Eur Heart J 2005;26:1719–25.
45. Hemingway H, Langenberg C, Damant J, Frost C, Pyörälä K, Barrett-Connor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. Circulation 2008;117:1526–36.
46. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979;59:8–13.
47. Addo J, Smeeth L, Leon DA. Hypertension in Sub-Saharan Africa: a systematic review. Hypertension 2007;50:1012–8.
48. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011;378:1297–305.
49. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983;67:968–77.
50. Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a metaanalysis. Addiction 2000;95:1505–23.
51. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. J Nutr 2006;136:2588–93.
52. Warensjö E, Jansson JH, Berglund L, et al. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction: a prospective case-control study. Br J Nutr 2004;91:635–42.
53. Mukuddem-Petersen J, Oosthuizen W, Jerling JC. A systematic review of the effects of nuts on blood lipid profiles in humans. J Nutr 2005;135:2082–9.
54. Kario K, McEwen BS, Pickering TG. Disasters and the heart: a review of the effects of earthquake-induced stress on cardiovascular disease. Hypertens Res 2003;26:355–67.
55. Voors AW, Johnson WD. Altitude and arteriosclerotic heart disease mortality in white residents of 99 of the 100 largest cities in the United States. J Chronic Dis 1979;32:157–62.
56. Kushi LH, Meyer KA, Jacobs DR Jr. Cereals, legumes, and chronic disease risk reduction: evidence from epidemiologic studies. Am J Clin Nutr 1999;70(Suppl 3):451s–8s.
57. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. Circulation 2010;121:2271–83.
58. McAfee A, McSorley E, Cuskelly G, et al. Red meat consumption: an overview of the risks and benefits. Meat Sci 2010;84:1–13.
59. Schwartz AR, Gerin W, Davidson KW, et al. Toward a causal model of cardiovascular responses to stress and the development of cardiovascular disease. Psychosom Med 2003;65:22–35.