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gSCIENCE

ORIGINAL RESEARCH

Assessing the Global Burden of Ischemic Heart Disease

Part 1: Methods for a Systematic Review of the Global Epidemiology of Ischemic Heart Disease in 1990 and 2010

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BACKGROUND Ischemic heart disease (IHD) is the leading cause of death worldwide. The GBD (Global Burden of Disease, Injuries, and Risk Factors) study (GBD 2010 Study) conducted a systematic review of IHD epidemiology literature from 1980 to 2008 to inform estimates of the burden on IHD in 21 world regions in 1990 and 2010.

METHODS The disease model of IHD for the GBD 2010 Study included IHD death and 3 sequelae: myocardial infarction, heart failure, and angina pectoris. Medline, EMBASE, and LILACS were searched for IHD epidemiology studies in GBD high-income and low- and middle-income regions published between 1980 and 2008 using a systematic protocol validated by regional IHD experts. Data from included studies were supplemented with unpublished data from selected high-quality surveillance and survey studies. The epidemiologic parameters of interest were incidence, prevalence, case fatality, and mortality.

RESULTS Literature searches yielded 40,205 unique papers, of which 1,801 met initial screening criteria. Upon detailed review of full text papers, 137 published studies were included. Unpublished data were obtained from 24 additional studies. Data were sufficient for high-income regions, but missing or sparse in many low- and middle-income regions, particularly Sub-Saharan Africa.

CONCLUSIONS A systematic review for the GBD 2010 Study provided IHD epidemiology estimates for most world regions, but highlighted the lack of information about IHD in Sub-Saharan Africa and other low-income regions. More complete knowledge of the global burden of IHD will require improved IHD surveillance programs in all world regions.

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Ischemic heart disease (IHD) is caused by insufficient oxygen delivery to meet the metabolic demands of heart muscle. IHD can be caused by a failure to adequately perfuse cardiac myocytes with oxygenated blood (failure of supply) and/or to increase myocyte oxygen demand [1]. Failure of oxygen supply most commonly occurs due to a fixed narrowing or acute rupture or dissection of an atherosclerotic coronary artery, or less commonly due to coronary artery spasm, embolism, or vasculitis. Inadequate oxygen supply may also occur due to severe anemia or systemic hypotension. Ischemia due to increased oxygen demand may be caused by sustained tachycardia, uncontrolled hypertension, or heart failure. Less commonly, IHD may occur due to cardiac revascularization procedures [1]. IHD can lead to acute myocardial necrosis (acute myocardial infarction [AMI]), fatal arrhythmia, or to a number of chronic sequelae, most prominently stable angina pectoris or heart failure (Fig. 1).

IHD was the leading cause of deaths and life-years lost from any cause worldwide in 2010 [2], and IHD was the leading cause of death and disability among the major cardiovascular diseases. IHD is not only a disease of the elderly in wealthy countries, but also past analyses by the GBD (Global Burden of Diseases, Injuries, and Risk Factors) study and other studies indicate that IHD has a major global impact on working-age adults and is a growing problem in low- and middle-income countries [3–5].

IHD is among the major diseases globally, but regional importance varies due to differences in IHD incidence, prevalence, and mortality, as well as the impact of competing diseases. The GBD study was started in 1991 as an effort to inform health policy making by using standard methods to comprehensively assess the mortality and disability burden of the world's major diseases, injuries, and risk factors by world region for the year 1990. GBD estimates were updated in 2004 [6], but the current study represents the first comprehensive and de novo analysis since the original study. The GBD embarked in 2007 to improve and update GBD methods and analyze the burden of diseases, risk factors, and injuries for the years 1990 and 2005 in 21 world regions (Fig. 2) [7]. The latest GBD analysis required comprehensive and systematic reviews of the epidemiologic literature for the major global diseases. Here, we present the methods and summary data for the GBD IHD epidemiology systematic review. The goals were to: 1) establish GBD case definitions for IHD and its sequelae; 2) define an epidemiologic model of IHD and data types to be included in the review; 3) document the systematic review methods including novel literature search and validation strategies; and 4) present the quantity and quality of the data retrieved.

IHD diagnosis and treatment have changed since the GBD last gathered primary epidemiologic data and established its IHD analysis methods. Most importantly, the universal case definition of MI [1,8] evolved to account for widespread use of biomarkers of MI [9] such as troponins [10] and creatine kinase-myocardial band mass, and cardiac imaging in high-income regions [11,12]. In regions where use of high-sensitivity biomarker measurement became common, many previously undiagnosed cases of AMI were identified. The advent of troponin measurements needs to be accounted for when estimating AMI incidence in high-income nations in 1990 and 2010, but troponin measurement cannot be required for AMI diagnosis in regions where troponin measurement is prohibitively expensive and are therefore not routinely performed [13].

Ongoing event surveillance of a defined population is the gold standard for obtaining accurate population-based IHD incidence and prevalence estimates. Outside of the MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) study [14], and a handful of similar surveillance studies [15,16], such estimates have been rare, especially in developing regions. The GBD Study has developed methods for estimating IHD epidemiologic parameters for regions with sparse data, but its estimated results will never substitute for rigorous and direct population surveillance. Therefore, this report will serve not only to quantify the available body of IHD epidemiologic research over the >25 years past, but it will also identify regional gaps in knowledge and highlight future challenges for global IHD epidemiology research.

METHODS

GBD 2005 study definitions of IHD. IHD may result in death or 3 general chronic sequelae: angina pectoris; nonfatal MI; or heart failure (Fig. 1).

IHD death. The *International Statistical Classification of Diseases and Related Health Problems* (ICD) is the international standard for classifying causes of death and nonfatal conditions. ICD rules require identification of the disease initiating the causal

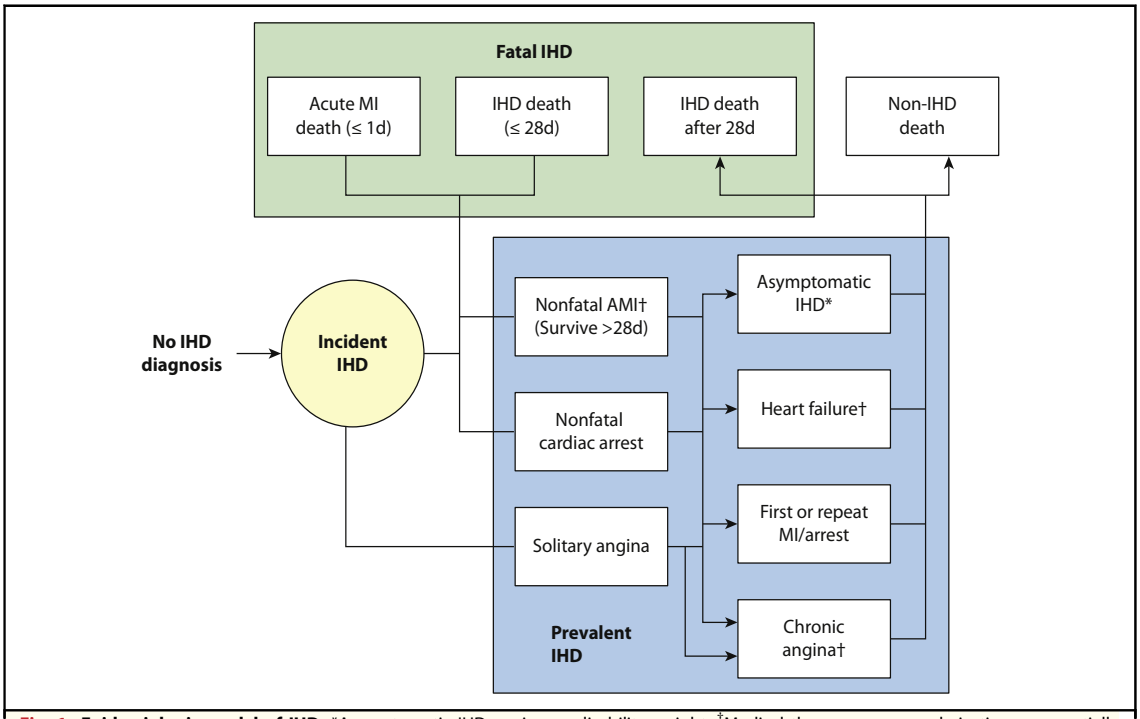

Fig. 1. Epidemiologic model of IHD. *Asymptomatic IHD carries no disability weight. †Medical therapy or revascularization may partially alleviate AMI, CHF, or angina symptoms. AMI, acute myocardial infarction; CHF, congestive heart failure; IHD, ischemic heart disease; MI, myocardial infarction.

chain ending in deaths—that is, the underlying cause of death. ICD codes identifying IHD as the underlying cause of death since 1950 were grouped under the subcategory "cardiovascular and circulatory diseases" within the category "noncommunicable diseases" as part of the GBD list of 56 major causes of death (Table 1). IHD has consistently been classified as an underlying cause of death across multiple revisions of the ICD over time [17]. IHD deaths typically fall into 1 of 2 broad categories: death attributable to AMI; and sudden cardiac deaths. Whereas AMI deaths usually meet a number of objective diagnostic criteria, many sudden cardiac deaths are not witnessed and their association with IHD can only be inferred [14,18].

The ICD also encompasses nonfatal conditions not meant to be underlying causes of death (e.g., essential hypertension) and conditions intermediate in the causal chain between an underlying cause and death (e.g., heart failure). When such codes are inappropriately listed as underlying causes of death on death certificates, they are termed "garbage codes" that need to be reassigned to legitimate underlying causes of death. Frequent use of garbage codes in some nations has led to underestimation of IHD mortality rates [19]. The GBD has developed methods for reallocating garbage codes to legitimate underlying causes of death [17]. Deaths assigned nonspecific cause, signs, and symptoms ICD codes not meant to represent underlying causes are allocated to legitimate underlying cause codes in proportions equal to the relative magnitude of underlying cause-, age-, and sex-specific death rates. For ICD conditions intermediate in the causal chain between an underlying cause and death, statistical methods, literature review, or expert opinion are used to distribute the garbage-coded deaths to causally associated underlying causes. Intermediate causes associated with IHD deaths are described in Table 1 and Supplemental Tables 1 and 2. Because IHD is the most prevalent cause of death worldwide, especially in older adults, and the biggest proportion of garbage codes are assigned to deaths in the elderly, a large proportion of garbage-coded deaths have been reallocated to IHD.

Nonfatal IHD sequelae. AMI is a sudden and sustained loss of perfusion to heart muscle resulting in cardiac necrosis. Prior GBD analyses followed past World Health Organization (WHO) MONICA study criteria [14], which required any 2 of the

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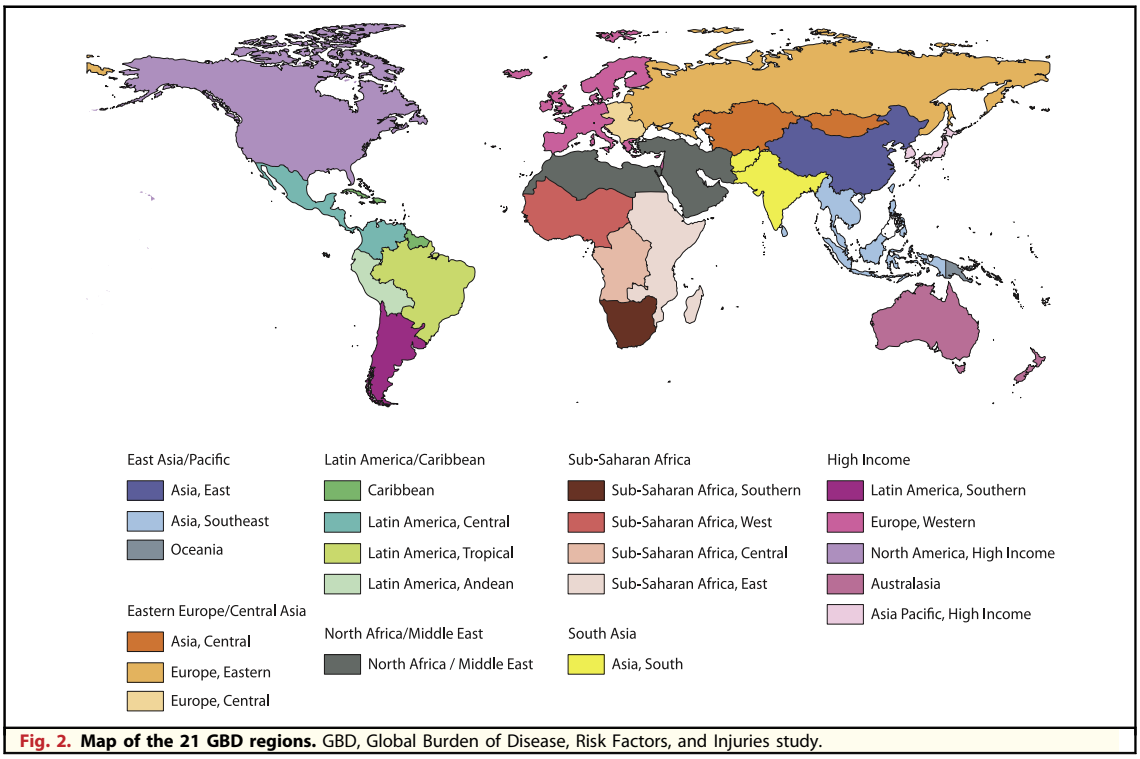

Fig. 2. Map of the 21 GBD regions. GBD, Global Burden of Disease, Risk Factors, and Injuries study.

following 3 criteria: ischemic symptoms; electrocardiographic changes; and elevated serum biomarkers. Newer biomarkers of cardiac ischemia, especially troponins, have improved the sensitivity of AMI diagnosis without a loss in specificity [9,10]. Another recent addition to the definition of AMI is evidence of perfusion or wall motion abnormalities, which depends on routine use of cardiac imaging technology (echocardiography, radionuclide scanning, angiography, or other technologies). Advances in AMI diagnostics led recent consensus panels to recommend a modified case definition of AMI based primarily on abnormal biomarker levels, especially troponins (Table 2) [1,8,13]. More AMI cases are diagnosed with the addition of the more sensitive troponin measures [20–23], leading to an apparent increase in AMI incidence without a change in the true incidence [18,24]. Trend analyses need to correct for the additional AMI diagnosed due to troponin measures in recent years in high-income regions [8]. The additional AMI cases identified using the new troponin-based criteria, but not captured by the old criteria may carry a prognosis no better than "old criteria" AMI, perhaps because the troponin-only cases occur more often in older patients with more comorbidities [18].

A potential consequence of an AMI definition more dependent on serum biomarkers and imaging (and less dependent on clinical symptoms) is a widening "diagnosis gap" between high-diagnostic capacity regions and low-diagnostic capacity regions. A WHO expert panel recently acknowledged this problem and proposed a 3-tiered definition of AMI (Table 2) [13]. WHO AMI category A is identical to the troponin-based European Society of Cardiology/American Heart Association/World Heart Federation definition and was the standard used by the GBD review for high-income regions. WHO AMI categories B and C were used as the standard for the GBD review for low- and middle-income region studies that lacked the resources necessary for cardiac biomarker measurement or cardiac imaging. It was decided a priori that GBD IHD analyses would have to adjust estimates at the individual study level for troponin measurement status.

The epidemiology of MI is best measured by capturing AMI cases at the time of diagnosis. Survey methods used to measure the prevalence of MI survivors (using self-reported diagnosis or resting electrocardiograph changes typical of past MI, especially Q waves) are subject to measurement error in low-incidence populations and past prevalent MI survey studies are of uneven quality [25]. Therefore, MI prevalence survey studies were not used directly to formulate GBD MI epidemiologic

Table 1. GBD cause of death and sequelae definitions for IHD

IHD Mortality	GBD Cause of Death Category	GBD Cause of Death Subcategory	ICD Classification
IHD mortality	Non-communicable diseases	Cardiovascular and circulatory disorders	ICD codes for IHD as underlying cause of death
			ICD-10 detail I20—I25
			ICD-10 tabulation 1 1,067 (I20—I25)
			ICD-9 detail 410—414
			ICD-9 tabulation—BTL B270, B278
			ICD-8 tabulation—A A083
			ICD-7 tabulation—A A081
			Categories of garbage-coded deaths frequently reallocated to IHD as the underlying cause of death
			Deaths assigned nonspecific symptoms or signs ICD codes*
			Deaths assigned to intermediate causes associated with IHD as the underlying cause†
IHD Sequelae (Disease States)	**Definition**		
AMI	Definite and possible AMI according to WHO guidelines (WHO category A, B, or C) (Table 2)		
Stable angina pectoris	Cases of clinically diagnosed stable exertional angina pectoris or definite angina pectoris according to Rose questionnaire (Supplemental Table 1), physician diagnosis, or taking nitrate medication for the relief of chest pain		
Congestive heart failure	Mild or greater symptomatic heart failure (Killip scale k2—k4 [54], NYHA stage II—IV [35], AHA/ACC stage C or D [55], or satisfying Framingham heart failure criteria) (Supplemental Table 2). Variable percentage attributed to IHD, regionally dependent on distribution of IHD as well as other causes of heart failure.		

ACC, American College of Cardiology; AHA, American Heart Association; AMI, acute myocardial infarction; GBD, Global Burden of Disease, Risk Factors, and Injuries study; ICD, International Statistical Classification of Diseases and Related Health Problems; IHD, ischemic heart disease; MI, myocardial infarction; NYHA, New York Heart Association; WHO, World Health Organization.

* Unspecified symptoms and signs ICD codes are not meant to be listed as underlying causes of death. Globally, the 20 most prevalent of these codes are ICD-10 R54, R99, R98, I46.9, R09.2, R96.0, I46.1, R68.8, R55, R96.1, N40, G43.9, M19.9, J06.9, R62.8 ,M25.9, G47.3, I46.0, R06, and R00.1 (details, Supplemental Table 1).

† Intermediate causes lie in the causal pathway between the underlying cause and death. ICD-10 intermediate cause codes associated with IHD as the underlying cause of death are I50, I51, I70, I10, I44, I49, I74, I99, G45.9, G93.1, J81, N17, N18, N19, R07.1, R07.2, R07.3, R07.4, R09.0, R40, R57.0, and R57.9 (details, Supplemental Table 2).

estimates. Silent MI occur without the usual signs and symptoms of an AMI but are recognized later using electrocardiography or imaging criteria for prior MI [26]. Because the GBD intends to quantify only deaths and symptomatic disease states, the GBD definition of prior MI excludes silent MI.

Angina pectoris is a pressure-like pain in the chest induced by exertion or stress and relieved within minutes after cessation of effort or treatment with antianginal medications. Stable angina is chest pain not associated with an acute coronary event that is induced reliably and reproducibly by the same level of exertion and is generally managed in the outpatient setting. Stable angina may be slightly (approximately 20%) more prevalent in women than in men internationally [27]. Unstable angina is a sudden and/or accelerating onset in chest pain or new chest pain at rest and represents a clinical state associated with high risk of AMI and death. In international registries, unstable angina historically constitutes approximately one-third to one-half of acute coronary syndrome presentations, but unstable angina has declined in use as an "acute coronary syndrome" category [28]. Subsequent IHD deaths or nonfatal MI in unstable angina patients were captured in either of the IHD mortality or MI categories.

Self-report of chest pain is subjective and there is no gold standard for estimating angina prevalence in most population surveys. The Rose questionnaire (Supplemental Table 3, sometimes referred to as the London School of Hygiene cardiovascular questionnaire), has been used as a standard community-based survey measure of angina prevalence. With

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Table 2. GBD case definitions for AMI, adapted from WHO 2008 to 2009 consensus panel definitions (adapted from Mendis et al. [13])

WHO Category A

When there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia (no evidence of a cause other than ischemia). Any 1 of the following criteria meets the diagnosis for MI.

1. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least 1 of the following:
   - 1.1 Symptoms of ischemia;*
   - 1.2 ECG changes indicative of new ischemia (new ST-T changes or new LBBB);†
   - 1.3 Development of pathological Q waves in the ECG,‡ including:
     - a. No unequivocal pathological Q waves in the first ECG or in event set of ECG followed by a record with a pathological Q wave;
     - *or*
     - b. Any Q-wave in leads V2 and V3 ≥0.02 s or QS complex in leads V2 and V3 or Q-wave ≥0.03 s and ≥0.01 mV deep or QS complex in leads I, II, aVL, aVF;
     - *or*
     - c. V4—V6 in any 2 leads of a contiguous lead grouping (I, aVL, V6; V4—V6; II, III, aVF).
   - 1.4 Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

   or
2. Sudden (abrupt) unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia;* and accompanied by
   - 2.1 Presumably new ST-segment elevation or new LBBB;†

   and/or
   - 2.2 Evidence of fresh thrombus by coronary angiography and/or at autopsy.

   But death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood, and there is no evidence of a noncoronary cause of death.

   or
3. Autopsy findings of an AMI.

WHO Category B

Whenever there is incomplete information on cardiac biomarkers (preferably troponin) and other diagnostic criteria needed to apply category A, the term MI should be used if:

Both of the following criteria are present:

- 1.1 Symptoms of ischemia;* and
- 1.2 Development of unequivocal pathological Q waves (no pathological Q-wave in the first ECG or in the event set of ECG] followed by a record with a pathological Q-wave);‡

or

Death with a history of coronary heart disease and/or documented cardiac pain within 72 h before death and no evidence of noncoronary cause of death, or autopsy evidence of chronic coronary heart disease, including coronary atherosclerosis and myocardial scarring.

WHO Category C

The term "probable MI" should be used when there is insufficient information to decide whether or not there was an MI based on definitions in categories A and B, but either 1 of the following is present in a person with symptoms of ischemia,* with no evidence of a noncoronary reason:

- 1.1 Development of unequivocal pathological Q waves (no pathological Q-wave in the first ECG or in the event set of ECG followed by a record with a pathological Q-wave‡ or development of new ischemia (new ST-T changes§ and an equivocal change in Q waves‖ demonstrated between the ECG associated with the event or between a previously recorded ECG and the event ECG);

or

- 1.2 Incomplete information on cardiac biomarkers (preferably troponin) provided that myocardial damage of other reasons and other clinical conditions that can cause a rise in cardiac biomarkers are excluded.

or

2. Autopsy findings are suggestive of MI but not conclusive.

aVF, automated volt foot; aVL, automated volt limb; ECG, electrocardiogram(s)/electrocardiography; LBBB, left bundle branch block; other abbreviations as in Table 1.

* Includes various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest; the discomfort usually lasts ≤20 min, often is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnea, diaphoresis, nausea or syncope.

† Minnesota codes: ST-segment depression: 4.1, 4.2; ST-segment elevation: 9.2; LBBB: 7.1.

‡ Minnesota codes: 1.1.1 through 1.2.5 plus 1.2.7. Specifically, any Q-wave in leads V2 andV3 ≥0.02 s (Minnesota code 1.2.1) or QS complex in leads V2 and V3 (Minnesota code 1.2.7). Q-wave ≥0.03 s and ≥0.1 mV deep (Minnesota codes 1.1.1, 1.2.2) or QS complex in leads I, II, aVL, aVF, or V4—V6 in any 2 leads of a contiguous lead grouping I, aVL, V6, V4—V6, II, III, aVF (Minnesota codes 1.1.7, 1.3.6).

§ Minnesota codes: 4.1; 4.2; 5.1; 5.2; 9.2.

‖ Minnesota code 1.2.8 or any 1.3 code.

evidence of inducible myocardial ischemia on exercise electrocardiogram plus nuclear coronary artery perfusion scanning as the gold standard of angina diagnosis, the Rose questionnaire has been found to have 40% to 67% sensitivity and 56% to 80% specificity, with markedly lower positive predictive value in women than in men [29,30]. It has been proposed that a higher portion of stable angina in women may be due to impaired coronary microcirculation not detectable with conventional coronary perfusion scans [27]. Nonetheless, because of the questionable accuracy of the Rose questionnaire, the GBD also reviewed surveys of physician-diagnosed angina reported by either the patient (survey respondent) or the physician. It was decided a priori that angina prevalence estimates would be adjusted at the individual study level for angina measurement method.

Anginal symptoms may be alleviated or diminished by antianginal medications, most commonly nitrates, beta-blockers, or calcium channel blockers. Alternately, anginal symptoms may be treated and partially or fully relieved by elective revascularization (i.e., percutaneous coronary interventions or coronary artery bypass graft surgery) (Fig. 1). Past GBD methods assumed revascularization led to complete remission of angina. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial randomized angina patients to either maximal pharmaceutical or pharmaceutical therapy plus revascularization demonstrated that either treatment completely relieved angina symptoms in at best 60% of patients in either treatment arm [14], so the present study assumed that medical management or coronary revascularization leads to complete remission in only a corresponding proportion of angina patients.

Heart failure is a chronic long-term sequela for IHD but may also result from hypertensive heart disease, valvular heart disease, or cardiomyopathies. The proportion of heart failure attributed to IHD as a cause varies by region [31] and has changed over time within regions [32]. The probability of developing heart failure after AMI was obtained from long-term follow-up studies of MI patients [33,34]. Over the past decades, most epidemiologic studies have based a diagnosis of heart failure on the functional classification developed by the New York Heart Association [35], Framingham Heart Study heart failure criteria [36] (Supplemental Table 4), or hospital discharge diagnosis ICD code. Framingham criteria are more rigorous, combining symptoms and physical examination. The GBD decided to capture only symptomatic cases of heart failure meeting Framingham criteria or inclusive of New York Heart Association class II or higher or hospitalized cases with heart failure as the principal discharge diagnosis (ICD-9 428, ICD-10 I50). Heart failure symptoms may be alleviated by diuretic and other medications, and survival time with heart failure can be prolonged by medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and others).

An epidemiologic model of IHD. For the purposes of identifying the main epidemiologic parameters involved with IHD and the diagnostic measures to target in the systematic review, we constructed an epidemiologic model of IHD based on the GBD definitions (Fig. 1). Causal arrows in the IHD model are unidirectional because there was an assumption that once a diagnosis of IHD is made, though symptoms may be alleviated, there is no complete remission to a state of not having IHD. "Asymptomatic IHD" describes persons who survived an initial IHD event and are living in an interval without symptoms of AMI, heart failure, or angina. Cardiac arrhythmias associated with IHD that occur outside the setting of AMI were described and measured by the GBD arrhythmia group and were not reviewed. As explained herein, some aspects of IHD are accounted for, but not specifically described in the model, such as unstable angina (because AMI following an episode of unstable angina would be captured in the model) or silent MI.

The GBD IHD disease model illustrates the inter-relation between IHD states: for persons in any given IHD state, there is a probability of transition to another IHD state (e.g., the probability of AMI after angina onset or the probability of heart failure after AMI) and a probability of dying (an IHD or non-IHD death). Standard relationships between disease model parameters (incidence, case fatality, mortality, and prevalence) were incorporated in a unique GBD software program, DisMod-MR (Disease Model Meta-Regression; Institute for Health Metrics and Evaluation, Seattle, WA, USA). DisMod-MR is particularly useful in imputing missing or incomplete estimates by fitting them to known estimates within a disease-specific model context. From the epidemiologic model, a list of the key epidemiologic parameters and study types were generated (Supplemental Table 5).

Summary methods for the systematic review of IHD epidemiology studies published from 1980 to 2008. Supplemental Appendix A and Figure 3 describe the systematic review methods in detail.

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In brief, 3 electronic databases were searched: MEDLINE (via PubMed), EMBASE, and LILACS. Searches were initially performed in MEDLINE and refined there before being adapted for EMBASE and LILACS. English language and non-English language articles were included; years were restricted to 1980 to 2008; articles were limited to human studies; and no age limits were applied. The PubMed search was performed using Medical Subject Heading (MeSH) terms related to IHD, and additional search terms related to IHD and IHD sequelae and geographic region terms were added to the search and restricted to the title or abstract of the citations. An inclusive, high-sensitivity approach was employed for low- and middle-income regions and a restrictive, high-specificity approach for high-income regions (Supplemental Appendix A). MeSH terms "developed" and "developing" were combined with specific country name key words in order to replicate GBD high-income and low- and middle-income region groupings. Comparable search strategies were executed in EMBASE and LILACS.

To validate the initial search strategy, selected IHD epidemiology experts representing 15 of the 21 GBD regions (Eastern Europe, East Asia, South Asia, North America, 4 Sub-Saharan Africa regions, Australasia, Middle East and North Africa, 4 Latin American regions, and the Caribbean) were asked to identify key IHD epidemiology papers from their region(s) of expertise published between January 1, 1980, and July 1, 2008. The initial electronic

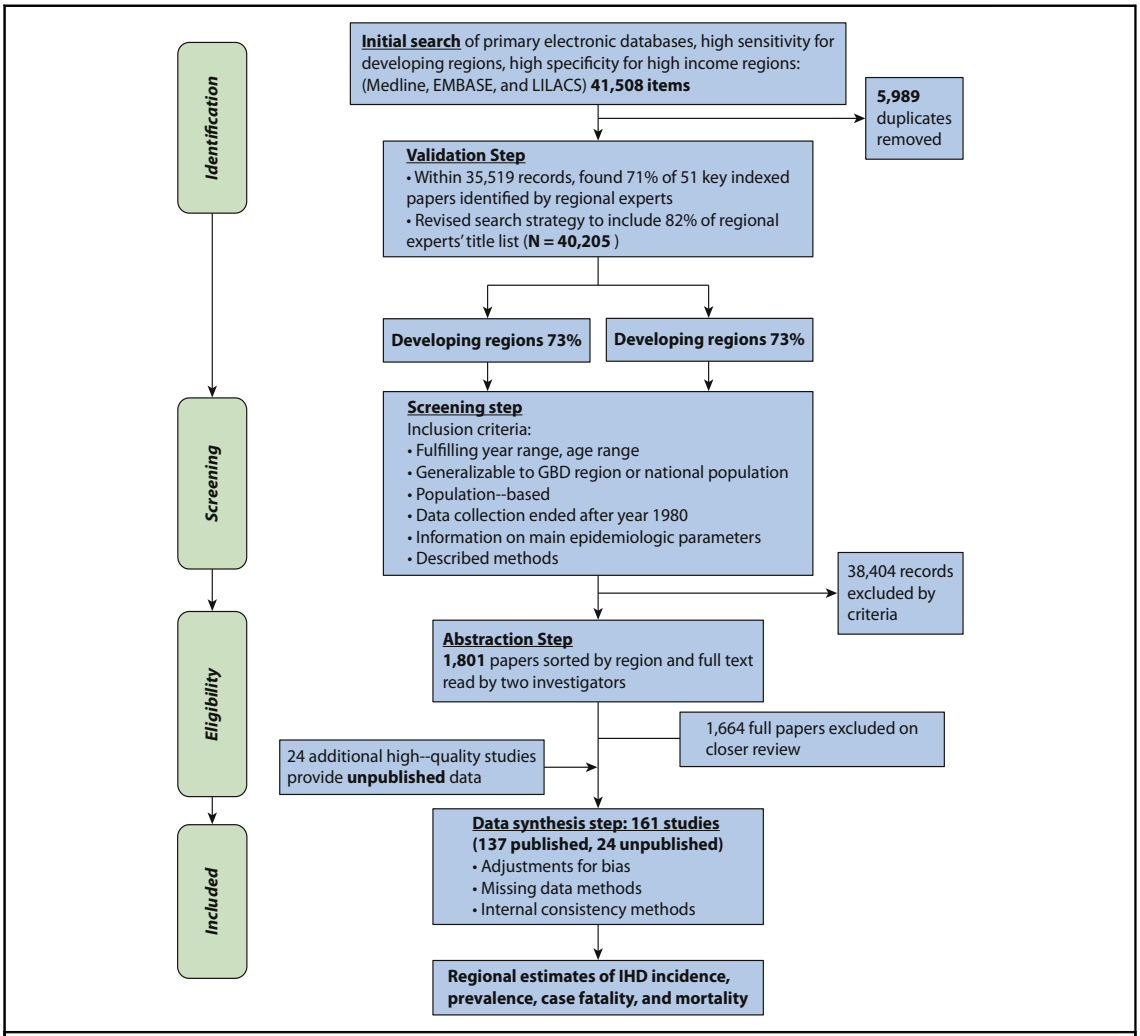

Fig. 3. Literature review and data abstraction flow chart for IHD systematic review. Abbreviations as in Figures 1 and 2.

database search results were checked against the final validation list of 51 key IHD studies submitted by the selected experts (Supplemental Appendix B). The initial search included 71% of the validation set papers. The initial search strategy was modified to include additional search terms identified in the expert panel's papers not retrieved in the first search. The electronic search was repeated in each of the 3 electronic databases, leading to inclusion of 82% of the experts' validation list.

Papers were selected for detailed full text review if the study met all of the following criteria: 1) it reported on an IHD epidemiologic parameter of interest to the GBD study (incidence, prevalence, case-fatality, or mortality); 2) it was population-based; 3) data was reported for an age range including at least 45 to 54 years; 4) the study observation period ended after 1980; 5) fatal IHD was defined using ICD or MONICA coding; and 6) nonfatal IHD conformed to one of the GBD IHD sequelae definitions. Pairs of study investigators personally reviewed eligible papers published in English, Spanish, Portuguese, or Chinese. Papers published in any other languages were translated by multilingual health researchers hired by the GBD study, and the resulting translations were reviewed by pairs of study investigators with the original paper's results in hand. Final inclusion or exclusion was based on the criteria stated herein, and papers were reviewed and discussed until consensus was reached about inclusion.

Inclusion of selected unpublished IHD epidemiology estimates. The gold standard for most of the IHD epidemiology estimates needed for the GBD study is a high-quality IHD surveillance study of a large, stable, geographically defined population representative of a GBD region. It was decided a priori in the interest of parsimony and quality assurance that epidemiologic estimates for the North America High Income, Western Europe, and East Asia regions would be derived primarily from high-quality surveillance or cohort studies that span the observation interval of interest (approximately 1980 until present). To obtain estimates surrounding the GBD target years of 1990 and 2005, 2 basic observation intervals were identified for pooled data: 1985 to 1997 and 1998 to present or most recent year.

For MONICA study data on IHD death and MI incidence, the first period of observation was defined as the period of the main MONICA study (approximately 1983 to 1993). Data after 1994 were contributed by ongoing surveillance studies that originated in MONICA sites in Sweden (north of country), Finland (FinRISK, national), Belgium (Ghent), Italy (Brianza), France (Strausbourg, Lille, and Toulouse), Lithuania (Kaunas), and China (Beijing, through to 2004) (Supplemental Table 6). Unpublished U.S. data (the ARIC [Atherosclerosis Risk in Communities Study], Framingham Heart Study, Cardiovascular Health Study, and others) were obtained from the National Heart, Lung, and Blood Institute (NHLBI) 2006 Chartbook [37]. Published estimates from the Rochester Epidemiology Project [15] and American Heart Association annual statistics reports [38] were also used. Unpublished national MI incidence data were also provided for Mexico (A. Lara Esqueda, September 2009), and Australia (T. Vos, June 2010).

To supplement stable angina prevalence data (especially for younger adults) and quantify the effect of different measurement methods on angina prevalence estimation, original analyses were conducted on the international WHS (World Health Survey) (2002 to 2004) [28], and 3 U.S. surveys: the BRFSS (Behavioral Risk Factor Surveillance System) (2005 to 2010) [24], the NHANES (National Health and Nutrition Examination Survey) (2001 to 2002, 2004 to 2009) [31], and the MEPS (Medical Expenditure Panel Survey) (2002 to 2009) [39]. Because the WHS provided angina prevalence data for 47 countries, most of them low- and middle-income countries, the WHS was a potentially valuable source of information on the pattern of angina prevalence worldwide. Information on the surveys and questionnaire questions used to identify stable angina cases in these surveys are listed in Supplemental Appendix C.

For the analysis of ischemic heart failure, hospital individual record data from Europe (European Hospital Morbidity Database, 1999 to 2007), United States (Healthcare Cost and Utilization Project and National Hospital Discharge Surveys, 1979 to 2006), Canada (Discharge Abstract Database, 2004 to 2009), Mexico (National Health Information System, 2000 to 2009), Ecuador (National Statistics Institute Database, 1996 to 2006), and Brazil (Hospital Information System of the National Unified Health System, 2006 to 2009) were analyzed to find the distribution of underlying heart failure causes in patients admitted with the principal diagnosis of heart failure. Additionally, deaths due to the major underlying causes of heart failure, as well as cases assigned heart failure as the cause of death from cause-of-death data, were used to inform the composition of heart failure causes.

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RESULTS

The final electronic search yielded 40,205 papers, of which 1,801 initially met inclusion criteria (Fig. 3). Careful review of full-text papers led to final inclusion of 137 studies (some studies' results were reported in more than one publication). Using 2012 World Bank country income categories [40], 114 high-income country studies, 77 middle-income country studies, and 15 low-income country studies were included (Supplemental Table 7). For published studies, 90 originated from high-income countries, 46 from middle-income countries, and one from low-income countries. All of the low-income countries studies reported on angina prevalence; there were no AMI or heart failure studies included from low-income countries. Despite extensive efforts to obtain full-text papers from both the Columbia University and Harvard University libraries and their affiliated collections or directly from regional experts, a number of publications were unobtainable. Most remarkably, in the Latin American and Caribbean regions, 56 full-text papers (3% of all eligible papers) were not retrievable: 97% of nonretrievable articles were indexed in LILACS and 78% were published prior to 1995. Unpublished data from 19 additional data sources on MI and heart failure epidemiology were added for the North America, Western Europe, Eastern Europe, Australasia, Central Latin America, Tropical Latin America, Andean Latin America, and East Asia regions. Angina prevalence estimates were obtained by study investigators for 18 GBD regions using the U.S. NHLBI 2006 Chartbook and population-weighted estimates from the WHS, BRFSS, NHANES, and MEPS surveys.

Sixty-two studies were included for MI incidence estimation, including 10 unpublished studies. With the exceptions of Central and Eastern Europe and East Asia, few good-quality studies on MI incidence were available representing low- and middle-income regions (Fig. 4). Especially in low- and middle-income regions, the majority of case-fatality studies were single-institution studies of in-hospital case fatality. Complete in- and out-of-hospital case fatality was rarely reported [41–45]. In the end, only 29 studies reporting on acute MI case fatality were included in the GBD analysis (Fig. 5).

IHD prevalence surveys were unusually common in the South Asia, Southeast Asia, Eastern Europe, and North Africa/Middle East regions. The systematic review yielded 42 studies reporting on stable angina prevalence. After adding the NHLBI Chartbook data, the WHS and 3 U.S. surveys analyzed for angina prevalence, led to 47 angina prevalence studies (Fig. 6). Of 42 heart failure studies used in the analysis, 9 were unpublished.

Sub-Saharan African regions, especially Central and East Africa, were remarkable for almost total lack of IHD epidemiology data of any type. Almost all of the IHD estimates for Sub-Saharan Africa came from South Africa. South Africa studies of IHD epidemiology exclusively in the white population (typical of studies published prior to the end of apartheid) were excluded because they were deemed not representative of the general population of the region. Until the advent of recent studies such as the Heart of Soweto Study [46], studies from Sub-Saharan Africa were all of low quality or complicated by uncertainty. For example, the only 2 IHD incidence papers for the entire region represented the township of Soweto, South Africa. The first incidence paper (Walker and Sareli [47]) did not state a case definition for IHD, and for both incidence estimates, the proportion of cases living in Soweto and the population of Soweto lack precise quantification [46,47]. The Eastern Europe region stood out because the majority of studies (75%) from that region sampled men only.

The only IHD incidence data spanning the years from approximately 1985 until 2005 using similar methods over time were gathered from following studies: 8 ongoing MONICA sites (Fin-MONICA [now FinAMI], Ghent-MONICA [Belgium], 3 French MONICA sites [Toulouse, Strasbourg, Lille], Brianza-MONICA [Italy], Sino-MONICA [Beijing, China], and Kaunas-MONICA [Lithuania]), the Northern Sweden surveillance study (not part of the original MONICA study, but employs MONICA methods), and in the United States, ARIC, the Framingham Heart Study, the Cardiovascular Health Study, and the Rochester Epidemiology Project.

Of the AMI incidence studies included, 4 of 7 high-income region studies gathering data after 2000 and reporting detailed diagnostic criteria included troponin measurements in their MI outcome diagnostic definitions. None of the developing region AMI incidence studies included positive troponin in the case definition of AMI.

DISCUSSION

Overview. A systematic review of IHD literature in 21 world regions demonstrated that it is feasible to gather IHD epidemiology literature using a high-sensitivity approach for developing regions

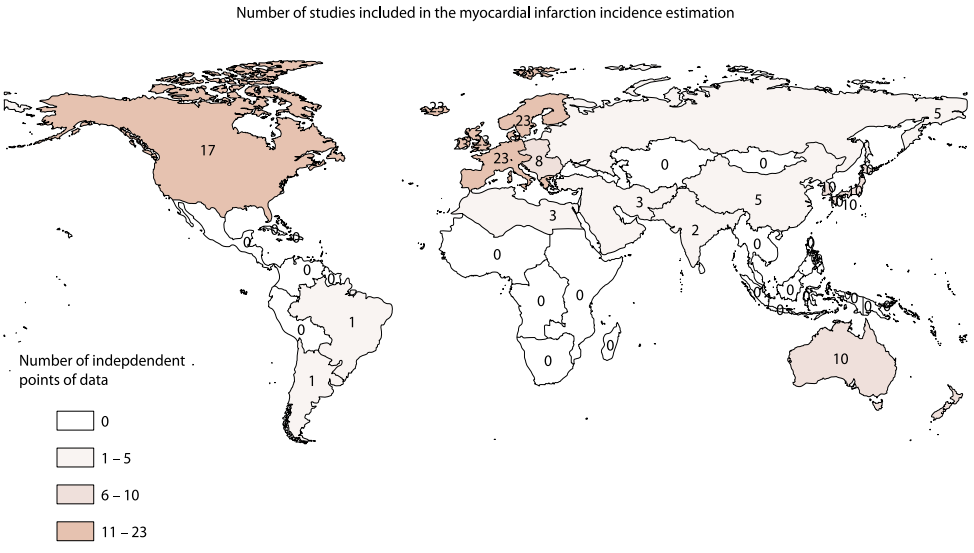

Fig. 4. Number of included studies used for myocardial infarction incidence estimation, by GBD region. GBD, Global Burden of Disease, Risk Factors, and Injuries study.

and a high-specificity approach for high-income regions. Despite this design, the review revealed scant IHD epidemiology data from most low- and middle-income regions, particularly Sub-Saharan Africa. In contrast, complete high-quality estimates were available from East Asia and Central Europe, which are on average middle-income regions. Even for high-income regions, most of the comprehensive estimates including the years surrounding 1990 and 2005 were gathered from unpublished data. From this review of IHD epidemiology, a number of key methodologic challenges were identified: the need to reallocate IHD deaths erroneously assigned to ill-defined cardiovascular causes, the need to adjust past incidence to fit with the new, troponin-based definition of AMI, measurement limitations of population survey estimation of stable angina and IHD prevalence, estimation of the fraction of all heart failure attributable to IHD and the more general problems of missing data, random error, and bias.

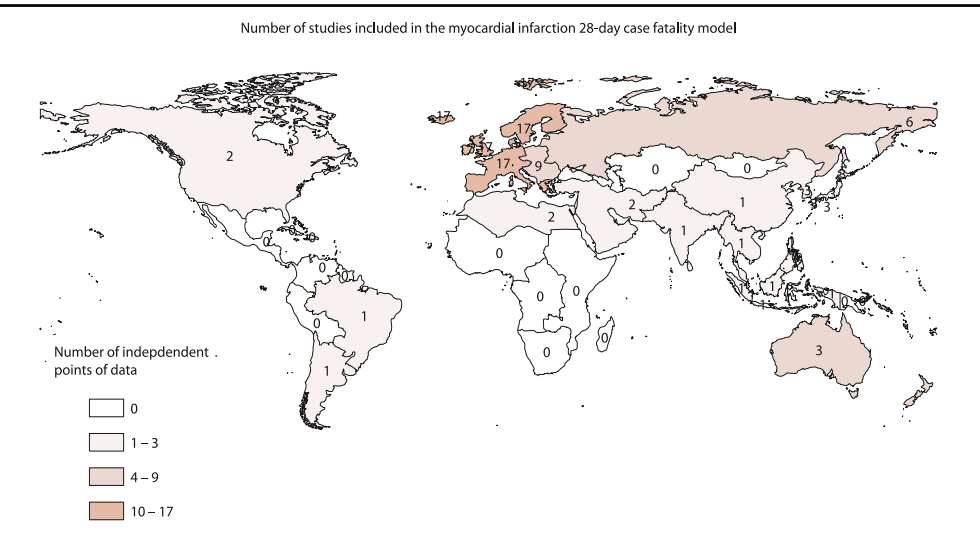

Fig. 5. Number of included studies used for acute myocardial infarction case fatality estimation, by GBD region. GBD, Global Burden of Disease, Risk Factors, and Injuries study.

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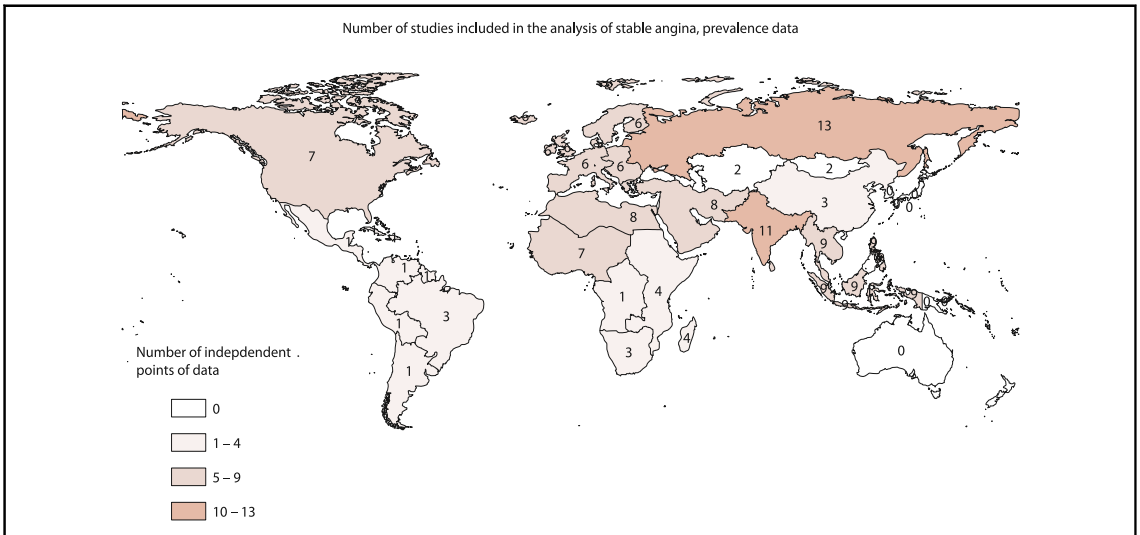

Fig. 6. Number of included studies used for stable angina pectoris prevalence estimation, by GBD region. GBD, Global Burden of Disease, Risk Factors, and Injuries study.

IHD death. Effective allocation of global public health resources depends on accurate vital statistics, including national cause-of-death data. The problem of "bridging" cause-of-death data across changing ICD definitions has been simplified by creating a list of GBD 291 major causes of death. GBD investigators have been able to consistently trace IHD as an underlying cause of death from the earliest ICD up until the current ICD-10. Frequent use of garbage codes may bias cause-specific mortality rates. In particular, past studies have shown that IHD death rates are substantially underestimated for some nations if garbage-coded deaths are not accounted for [19]. The GBD has recently refined the method for reallocating garbage-coded deaths to IHD and other underlying causes [17], ensuring optimal use of available national cause-of-death data for the purpose of estimating the mortality portion of the global burden of IHD.

AMI. The recommended case definition of AMI was recently changed to include a primary emphasis on positive biomarker measurements, specifically troponin [1]. Troponin measurements were introduced in high-income nations during the mid-1990s. We found no low- or middle-income region studies of AMI incorporating positive troponin in the case definition published during 1980 to 2008. Even in high-income regions, the troponin-based definition of MI has been used in epidemiologic studies only since approximately 2000. Moving forward, in comparing past AMI incidence estimates to estimates after 2000, past estimates will require adjustment to reflect the additional incidence that would have been added had troponin been available [48,49]. The GBD main epidemiologic and burden estimates will adjust AMI incidence using a study-level troponin measurement variable for data published after approximately 2000. Regarding MI case fatality, numerous published single-center studies of in-hospital case fatality were identified, but population-based and multicenter studies were rare, leading to only 29 AMI case-fatality studies included in the analysis; 15 of these were from low- or middle-income regions.

Angina pectoris. The primary GBD angina case definition relies on the classic Rose questionnaire descriptions, but studies included from the systematic review employed a variety of measures of angina prevalence, including self-reported diagnosis, diagnosis made by a study physician, and even use of specific antianginal medications (e.g., nitrates). Several studies suggest that the Rose questionnaire has poor specificity, especially in women (range 56% to 76%) [29,50,51], leading to inflated prevalence estimates in women than in men. Others argue that higher angina prevalence in women than in men persists when a more rigorous diagnostic method is used [52], and Rose-diagnosed angina implies a poor prognosis and should not be dismissed by clinicians or epidemiologists [27]. Based on the review literature, we concluded that angina prevalence estimation should account for measurement method and that lack of

a diagnostic gold standard calls for caution in interpreting estimates of angina prevalence.

Ischemic heart failure. IHD is only one of several causes of heart failure in the GBD. Estimation of ischemic heart failure prevalence required a 2-step process: 1) estimating the total heart failure envelope, inclusive of heart failure cases of all causal origins; and 2) estimating the proportion of heart failure attributable to IHD specific to region, age group, and sex. Data from the systematic review were included in both steps of the analysis.

Study limitations. Though this systematic review conformed to most of the standard guidelines for systematic reviews (PRISMA checklist Supplemental Appendix D) [53], it is possible that many of the included studies reported data collected with bias, and for many estimates, no measures of uncertainty (in the form of standard deviations or errors, confidence intervals, etc.) were reported. Though many of the studies contributing data to the GBD review were population-based studies or national cause-of-death or hospital registries, some may not be regionally representative. In some instances, national or provincial surveys or cohort studies were selected that may fail to accurately represent an epidemiologically heterogeneous regional population. A study of national IHD mortality trends in several selected world regions demonstrated that there may be variability within broad geographic regions [54]. Some of this variance may be due to methodologic differences in vital statistics registration, but some may be due to epidemiologic heterogeneity that is obscured when reporting estimates for broad regions. Especially for publications from the Latin American and Caribbean region papers published before 1995, a substantial proportion of published papers selected for review were not obtainable. Selected unpublished data were obtained, but these predominantly represent high-income regions. It is likely that we are missing a great deal of unpublished data from government and large health system records; it was beyond the scope of this review to quantify the volume of unpublished data missed by using standard electronic database search methods.

CONCLUSIONS

Health policy decisions and resource allocation are ideally made based on high-quality epidemiologic data. The scale and pervasiveness of IHD in the majority of world regions makes estimation of IHD mortality, incidence, prevalence, and case fatality crucially important to public health worldwide. A main objective of the GBD is provision of accurate, unbiased estimates of disease burden gathered and analyzed with standard methods and reported with transparency. This GBD systematic review of IHD demonstrated that it is feasible to complete a large-scale review of the IHD epidemiology literature using search methods tailored to emphasize sensitivity in developing regions and specificity in high-income regions. Despite this broad search and careful screening, the quantitative results of the review demonstrate the scarcity of high-quality IHD epidemiologic data to support policy making and resource allocation, particularly in low- and middle-income regions. Assessment of qualitative results of the IHD epidemiology review leads to the conclusion that there is no substitute for high-quality, standardized surveillance studies of IHD. Ongoing surveillance studies deserve support, and the founding of new surveillance studies should be a high priority, especially in low- and middle-income regions.

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SUPPLEMENTAL DATA

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.gheart.2012.10.004

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