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Correspondence to: Dr. Louise Pilote, Divisions of Internal Medicine and Clinical Epidemiology, Rm. A4.23, McGill University Health Centre Research Institute, 687 av. Des Pins Ouest, Montréal QC H3A 1A1; fax 514 934-8293; louise.pilote@mcgill.ca

The GENESIS investigators who coauthored the supplement are: Louise Pilote and Kaberi Dasgupta, Divisions of Internal Medicine and Clinical Epidemiology, and Danielle Libersan, Division of Clinical Epidemiology, The McGill University Health Centre Research Institute, McGill University, Montréal, Que.; Veena Guru, Division of Cardiovascular Surgery, Sunnybrook and Women's College Health Sciences Centre, Institute for Clinical Evaluative Sciences, University of Toronto, Toronto, Ont.; Karin H. Humphries, Centre for Health Evaluation and Outcome Sciences,

St. Paul's Hospital, University of British Columbia, Vancouver, BC; Jennifer McGrath, Department of Psychology, Concordia University, Montréal, Que.; Colleen Norris, University of Alberta, Edmonton, Alta.; Doreen Rabi and William Amin Ghali, Department of Medicine and Community Health Sciences, University of Calgary, Calgary, Alta.; Johanne Tremblay, Pavel Hamet and Milan Petrovich, Centre hospitalier de l'Université de Montréal Research Centre, Hôtel-Dieu, Université de Montréal, Montréal, Que.; Tracie Barnett and Jennifer O'Loughlin, Groupe de recherche interdisciplinaire en santé, Département de médecine sociale et préventive, Université de Montréal, Montréal, Que.; Arsham Alamian and Gilles Paradis, Institut national de santé publique du Québec, Québec, Que.; Jafna Cox, New Halifax Infirmary Site, QEII Health Sciences Center, Dalhousie University, Halifax, NS; Sherry Grace, York University, University Health Network, Toronto, Ont.; Teresa Ho, Department of Epidemiology and Biostatistics, McGill University, Montréal, Que.; Susan Kirkland, Department of Community Health and Epidemiology, Dalhousie University, Halifax, NS; Marie Lambert, Département de pédiatrie, Hôpital Ste-Justine and University of Montreal, Montréal, Que.; and Vicky Tagalakakis, Centre for Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montréal, Que.

Women and cardiovascular disease

Elizabeth Barrett-Connor

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Cardiovascular disease is responsible for half of all deaths among women aged 50 and older in Canada and the United States. Nevertheless, women have less heart disease than men. Perhaps this is the main reason why the study of heart disease in women is a relatively recent phenomenon. In the last few years interest has increased (in parallel with increasing numbers of female scientists), evidenced by the recent publication of at least 3 books on the subject of cardiovascular disease in women.^{1–3} This increased interest appears to have prompted the timely publication of the *CMAJ* supplement “A comprehensive view of sex-specific issues related to cardiovascular disease” (available online at www.cmaj.ca/cgi/content/full/176/6/S1).⁴ The 480 mainly recent references cited in the supplement are further evidence of the increased interest in this area. In addition to highlighting the relevance of this issue, the reviews contained in the supplement illustrate the many information gaps facing health care professionals and decision-makers. In this commentary, I have taken the liberty of highlighting some of

the deficiencies in the literature, through the critical appraisal of key articles cited in the supplement, as well as some deficiencies in the review itself.

After many years of studies restricted to men or without sex-specific analyses, there are surprisingly few original sex-specific studies in the same cohort. For the first paper in the *CMAJ* supplement, “Burden of cardiovascular disease in women and men” (page S1), Rabi and Cox performed a systematic review of published cohort, case-control or case-cohort studies of prevalence, incidence and mortality related to cardiovascular disease, atrial fibrillation and congestive heart failure in women and men.⁴ It is notable that only 33 original articles were found that presented data on any of these outcomes in both sexes.

Many papers have been written about the decline in cardiovascular disease among men but not among women over several decades, with the inference that men receive more preventive and therapeutic medicine. In their systematic review, Rabi and Cox cite 3 different papers reporting cardiovascular

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mortality over time, 1965–1972, 1980–1984 and 1990–2000. The interpretation of these data requires that the reader know whether the data are numbers or rates, and are or are not age-adjusted. This problem is illustrated by Fig. 1, perhaps the most widely printed and misunderstood graphic on cardiovascular mortality trends in the United States. As shown, between 1979 and 2000, there were successively fewer deaths from cardiovascular disease among men and successively more deaths from this cause among women. This figure shows numbers, not rates, and therefore is relevant to the health care burden, but not to the preferential application of modern medicine to men. In fact, the incidence and the case-fatality rate of coronary artery disease has declined in both sexes, by 63% among men and by 60% among women.⁵

In the paper entitled “Cardiovascular risk factors in girls and boys” (page S5), McGrath and coauthors report on their review of cross-sectional surveys in Canada and the United States, with puzzling findings.⁴ Despite increasing obesity over time, youth in Canada (and the United States) showed no change in low-density or high-density lipoprotein cholesterol levels, a 10% decrease in triglyceride levels and a 3% decrease in blood glucose levels. One plausible explanation for this paradox is that Canadian youth may have increased their physical activity. Exercise is less likely to explain the US data, where most children attend schools that have dropped or decreased their physical education programs.

Another paper, by Dasgupta and coauthors, reviews the striking differences in adult obesity between Canada and the United States (page S12).⁴ The proportion of Canadian adults who are overweight (body mass index ≥ 25) remained stable at 48% from 1994 to 2001. In contrast, the proportion of overweight adults in the United States dramatically increased since 1988, to almost 65% in 1999.⁵ Dasgupta and coauthors paid surprisingly little attention to the fact that men have more central obesity (waist girth) and women have more hip and thigh girth. Central obesity is a more important risk factor for cardiovascular disease than body mass index in both sexes and is thought to explain at least part of the sex-specific differences in

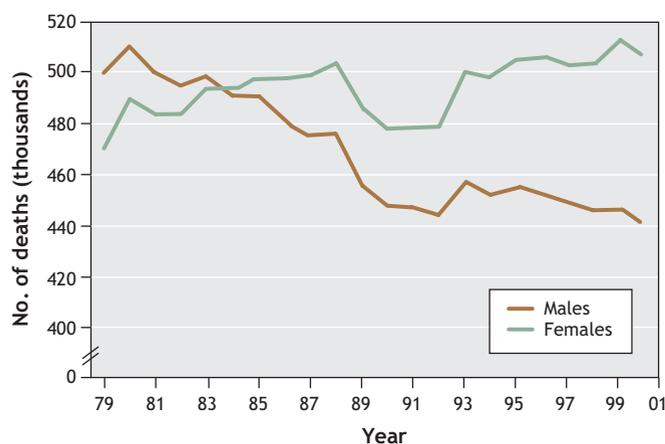


Fig. 1: Cardiovascular mortality trends among men and women in the United States, 1979–2000. Source: US Centers for Disease Control and Prevention / National Center for Health Statistics.

cardiovascular disease. As an alternative explanation, a cardio-protective role for hip and buttock fat has not been excluded.

Studies to date have shown no important differences in the relative risk of cardiovascular disease associated with most classic risk factors but striking differences in the absolute risk, favouring women at any given level of a risk factor. Diabetes is different: it increases the risk of cardiovascular disease among women to a greater extent than it does among men. The sex-specific effect of diabetes on cardiovascular mortality may be explained in part by the more common clustering of multiple risk factors in diabetic women compared with nondiabetic women than seen in diabetic men compared with nondiabetic men. Several studies have highlighted the importance of post-challenge hyperglycemia as being more strongly associated with cardiovascular disease than fasting glucose in both sexes.⁶ However, the issue of labelling someone with a risk factor such as being “prediabetic” was not discussed in depth. From a public-policy perspective, it is unclear whether it is practical or cost-effective to implement a different diagnostic standard, despite the increase in accuracy of the post-challenge test.

The limited data on sex-specific differences in prodrome or presentation of myocardial infarction are well described in the paper “Differences in cardiovascular presentation in women and men” (page S22).⁴ The results from these mostly retrospective studies are difficult to interpret. Questions about prodrome in either sex suffer from a lack of an appropriate comparison group. If a patient recalls excess fatigue in the month before the heart attack, what is the prevalence of fatigue in that month among people of the same age and sex without a heart attack? With regard to symptoms, the questions routinely asked of women (for research or in the emergency department) are those based on men’s symptoms. One recent study suggests that men report more severe chest pain and sweating and that women report less severe pain and more nausea.⁷ Because physicians know that women with chest pain are less likely than men with chest pain to be having a heart attack, women with atypical symptoms and no severe chest pain are more likely to remain undiagnosed and therefore not contribute to data on the prevalence or characteristics of atypical presentation. Population-based studies showing that women have more “silent myocardial infarction” than men (based on electrocardiography) support this assumption.⁸ This is obviously an area ripe for prospective studies.

Validation of diagnostic tests for coronary artery disease is often accomplished during clinical trials and is therefore less complete for women than for men. Women with ischemic heart disease who seek medical attention undergo less diagnostic testing than men do with the same symptoms. Stress tests are said to be less useful in women than in men, but the failure may not be in the test itself: the positive predictive value of a diagnostic test increases as the prevalence of disease increases, and women’s prior probability of first heart attack is lower than that of men’s.

As reviewed by Guru and coauthors in “Delivery of cardiac care in women and men” (page S26),⁴ women with acute myocardial infarction are less apt than men to receive thrombolysis or revascularization. These sex-specific differences

may be appropriate when women are older and have significant comorbidity. The authors cite papers showing no sex bias in treatment allocation and reperfusion when data are controlled for other factors. Data from Canada also show no evidence of sex-specific differences in secondary prevention based on prescriptions for evidence-based medication. However, older patients are less likely than younger patients to receive such medication, and about 45% of patients with acute myocardial infarction aged 65 and older are women. Women participate less often than men in rehabilitation programs, which might reflect more depressed mood or more responsibility for other household members. Similar to most reports from the United States, women in Canada are less likely than men to undergo coronary artery revascularization, differences attributed to their greater operative risk.

In the paper “Outcomes of CVD in women and men — clinical trials” (page S29),⁴ Humphries and coauthors report that clinical trials of the efficacy of thrombolysis have shown similar benefits in women and men after adjustment for baseline differences, but a greater risk of bleeding in women. A published meta-analysis showed significantly better outcomes with percutaneous coronary intervention than with thrombolysis in both sexes combined, but sex-specific outcomes were not reported. Results of studies of coronary artery bypass grafting suggest that women have poorer short-term but not long-term prognosis than men do; women’s postoperative mortality has decreased more than men’s over time. Differences between Canada and the United States in the age-adjusted rates of death from coronary artery disease are greater than the sex-specific differences within the countries, with much lower rates in Canada despite the much higher use of revascularization procedures in the United States, as shown in Table 16 of the supplement (page S28).⁴

In the paper “Outcomes of CVD in women and men — post-admission drug therapy” (page S33), sex-specific differences in the effects of medical treatment are surprisingly few, given that women are usually prescribed the same dose of medication as that prescribed for men, despite their smaller body size and different percent body fat. Several trials reporting that medications were effective only in men often had inadequate power owing to the small proportion of women in these trials, usually 25%–35%.

The authors note differences between women and men in the use of anticoagulants and antiplatelet agents (page S33). In the largest clinical trial, acetylsalicylic acid reduced the risk of stroke, but not of myocardial infarction, among women.⁹ Only 1 of 3 trials of the platelet inhibitor glycoprotein IIb/IIIa reported sex-specific data; this trial showed benefit in men and harm in women. In an analysis of pooled data from 5 warfarin trials, warfarin was found to reduce the risk of stroke in both sexes; women had more benefit but more major bleeding.

Despite the extensive work undertaken by this multidisciplinary group, the supplement does not address other highly relevant but poorly understood observations. For example, it is unclear why the universal sex-specific difference is restricted to coronary artery disease and does not extend to stroke or to lower-extremity arterial disease. Also, there is

only one unreferenced paragraph on the possible etiologic reasons for the sex-specific differences in heart disease. There is also limited discussion on the interrelation between socioeconomic status and sex-specific differences in cardiovascular disease. It seems that most of the evidence of an interrelation between sex and socioeconomic status for both cardiovascular disease and its risk factors comes from studies involving men. The authors refer to only 3 papers with sex-specific data, 2 from Sweden and 1 from the United States. In the US report, low socioeconomic status had a much larger effect on cardiovascular disease risk among women than among men, differences that were not explained by social class differences in risk factors. Assuming these are the best data, we still do not know whether the socioeconomic differences reflect differences in stress, education, occupation or income within job classification (women typically are paid less than men for the same job).

The strengths of this supplement include the use of well-described systematic literature searches in most of the papers. The enormity of the undertaking provides the reader with a comprehensive review of the topic. On occasion, however, details such as the search criteria and the years covered by the review were not explicitly described.

This supplement should serve to clarify important research priorities for Canadians and the international community. I expect that this overview of the literature will also provide a framework upon which to improve research on existing data and initiate new research.

This article has been peer reviewed.

Elizabeth Barrett-Connor is with the Department of Family and Preventive Medicine, University of California at San Diego, La Jolla, Calif.

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Correspondence to: Dr. Elizabeth Barrett-Connor, Department of Family and Preventive Medicine, University of California at San Diego, 9500 Gilman Dr., La Jolla CA 92093-0607; fax 858 534-8625; ebarrettconnor@ucsd.edu