Journal of Diabetes and Its Complications 28 (2014) 791–797

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Diabetes mellitus and mortality from all-causes, cancer, cardiovascular and respiratory disease: Evidence from the Health Survey for England and Scottish Health Survey cohorts

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ARTICLE INFO

Article history:
Received 23 April 2014
Received in revised form 3 June 2014
Accepted 25 June 2014
Available online 1 July 2014

Keywords:
Diabetes
All-cause
Cardiovascular disease
Cancer
Respiratory disease

ABSTRACT

Background: Diabetes mellitus is associated with differing rates of all-cause and cause-specific mortality compared with the general population; although the strength of these associations requires further investigation. The effects of confounding factors, such as overweight and obesity and the presence of co-morbid cardiovascular disease (CVD), upon such associations also remain unclear. There is thus a need for studies which utilise data from nationally-representative samples to explore these associations further.
Methods: A cohort study of 204,533 participants aged 16+ years (7,199 with diabetes) from the Health Survey for England (HSE) (1994–2008) and Scottish Health Survey (SHeS) (1995, 1998 and 2003) linked with UK mortality records. Odds ratios (ORs) of all-cause and cause-specific mortality and 95% confidence intervals were estimated using logistic and multinomial logistic regression.
Results: There were 20,051 deaths (1,814 among those with diabetes). Adjusted (age, sex, and smoking status) ORs for all-cause mortality among those with diabetes was 1.68 (95%CI 1.57–1.79). Cause-specific mortality ORs were: cancer 1.26 (1.13–1.42), respiratory diseases 1.25 (1.08–1.46), CVD 1.96 (1.80–2.14) and 'other' causes 2.06 (1.84–2.30). These were not attenuated significantly after adjustment for generalised and/or central adiposity and other confounding factors. The odds of mortality differed between those with and without comorbid CVD at baseline; the ORs for the latter group were substantially increased.
Conclusions: In addition to the excess in CVD and all-cause mortality among those with diabetes, there is also increased mortality from cancer, respiratory diseases, and 'other' causes. This increase in mortality is independent of obesity and a range of other confounding factors. With falling CVD incidence and mortality, the raised risks of respiratory and cancer deaths in people with diabetes will become more important and require increased health care provision.

1. Introduction

Globally, more than 366 million individuals currently live with diabetes mellitus, with this figure expected to rise to 552 million by 2030 (Whiting, Guariguata, Weil, & Shaw, 2011). The World Health Organization estimates that around 1.1 million deaths occur per year as a result of the disease (World Health Organization, 2011). Around 2.9 million individuals in England currently have diagnosed diabetes, a prevalence of 4.5% (NHS & The Information Centre, 2011). Projections for England estimate that by 2030 over 4.5 million people will be living with diabetes (APHO, 2011). The number of individuals living with diabetes means that if there was found to be an excess in mortality caused by the disease, this could result in a large number of premature deaths.

The association between diabetes and increased all-cause mortality, particularly from cardiovascular disease (CVD) and renal disease, is well recognised. However, there is heterogeneity between studies for some specific causes of death, particularly in relation to cancer (Renehan et al., 2012). Some studies have found cancer mortality rates similar to those within the general population (De Marco et al., 1999; Laing et al., 1999), while others show an increase (Dawson, Willis, Florkowski, & Scott, 2008; Guzder, Gatling, Mullee, & Byrne, 2007; Zhou et al., 2010) or decrease (Sasaki, Kamado, & Uehara, 1994; Wong, Pearson, Murchison, Williams, & Narayan, 1991) among people with diabetes; most recent studies have found an increase, including those from Europe and the United States. The Emerging Risk Factors Collaboration (ERFC) study analysed pooled data from 97 prospective studies (including >800,000 participants) and found increased cancer mortality among those with diabetes (hazard ratio (HR) 1.25, 95%

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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http://dx.doi.org/10.1016/j.jdiacomp.2014.06.016
1056-8727/

CI 1.19–1.31) (Seshasai et al., 2011). Investigations of site-specific cancers also demonstrate differences in mortality risk among those with diabetes (Batty, Shipley, Marmot, & Smith, 2004; Dawson et al., 2008; Verlato, Zoppini, Bonora, & Muggeo, 2003). Studies consistently find increased pancreatic cancer mortality among those with diabetes, but whether this is due only to reverse causality is still uncertain (Calle, Murphy, Rodriguez, Thun, & Heath, 1998). Evidence also demonstrates increased risks for bladder, liver and breast cancer mortality (Coughlin, Calle, Teras, Petrelli, & Thun, 2004). Analysis of Whitehall I data found no significant association between diabetes and colorectal cancer (Morrison et al., 2011). Chia et al. further found that women with diabetes subsequently diagnosed with endometrial cancer experienced a 70% increase in all-cause mortality but not mortality from endometrial cancer (Chia, Newcomb, Trentham-Dietz, & Hampton, 2007). There are also mixed findings related to cancer incidence (all-cause and site-specific) (Atchison, Gridley, Carreon, Leitzmann, & McGlynn, 2011; Giovannucci et al., 2010).

There is a limited amount of evidence relating to diabetes and respiratory disease mortality (Dawson et al., 2008; De Marco et al., 1999; Murugan & Sharma, 2008). Current evidence suggests a biological link between inflammation, reduced levels of adiponectin within the body and the development of diabetes and respiratory disease (Sevenoaks & Stockley, 2006). A correlation has also been found between measurements of abdominal obesity and respiratory conditions (Zammit, Liddicoat, Moonsie, & Makker, 2010).

The need for national studies exploring the association between diabetes and cause-specific mortality is highlighted by differences in the strength of the associations between countries (Morrish, Wang, Stevens, Fuller, & Keen, 2001). De Marco et al. concluded that these may be caused by differences in the severity of diabetes or differing national treatment cultures (De Marco et al., 1999). Therefore, research is required that further explores the association between diabetes and mortality from cancer and respiratory disease. Current research indicates that, for mortality from a number of causes, it may be diabetes-related comorbidities that increase an individual's risk of death rather than diabetes itself. (Mohammadi et al., 2007) This paper examines associations between diabetes and a range of causes of mortality but also assesses the contribution to the associations of overweight/obesity, social class and region, and the presence of comorbidities.

2. Materials and methods

2.1. Participants and data

Study participants were adults within the Health Survey for England (HSE) or Scottish Health Survey (SHeS) who gave permission for their data to be flagged with national mortality data. Detailed descriptions of the HSE and SHeS have been reported elsewhere (Gray et al., 2010; Mindell et al., 2012). The surveys select a random, nationally representative, general population sample (with a different sample selected each year). All participants were visited by an interviewer, who asks questions related to health and lifestyle behaviour, requests consent for data linkage to administrative datasets, and measures weight and height. If the participant agreed, a nurse visited to collect further physical measurements (including waist and hip circumference), biological samples and information about prescribed medications.

Within the HSE and SHeS, participants with diabetes were identified via at least one of three variables: the participant volunteered diabetes as a longstanding illness, or a positive response to a diabetes-specific question (only available in some years) or a diabetes-related prescribed medication was recorded by the nurse. Individuals with CVD were identified after volunteering a positive response to the longstanding illness question (as with diabetes).

Data from HSE years 1994–2008 and SHES years 1995, 1998 and 2003 linked to UK mortality data up to March 2011 were analysed. Participants were asked to consent to survey data linkage, with consent rates ranging from 80% to 95%. Mortality records were available only for deaths that occurred within the UK. Variables were created for cancer (C00-C97), respiratory diseases (J00-J99) and CVD (ICD10 codes I00-I99); 'other' causes included all remaining deaths.

A raised waist circumference was defined as >102 cm for men and >88 cm for women (World Health Organization, 2008). As there is no consensus for thresholds for a raised waist-to-hip ratio (Molarius & Seidell, 1998), those used within the HSE since 1997 were selected: >0.949 for men and >0.849 for women. Raised glycated haemoglobin (HbA_{1C}) was considered to be >6.49 mmol/mol. In total 28,754 individuals within the study had a measurement for glycated haemoglobin. Although this biomarker was adjusted for within the regression models, because the focus of the study was an exploration of the potential excess mortality among those with doctor diagnosed diabetes compared with the general population, it was not used to identify those with undiagnosed diabetes. Region was divided into four areas (South, Midlands, North, and Scotland) and education into three groups (degree or equivalent level, other, no qualifications). Social class was separated into seven groups based upon the Registrar-General's Social Class based on occupation bandings (I: professional occupations, II: managerial and technical, IIINM: skilled non-manual, IIIM: skilled manual, IV: partly-skilled, V: unskilled and other).

One hundred forty-seven cases were excluded from the analyses due to missing data for age or gender; survey participants reporting cancer at baseline were also excluded (n = 3,656), leaving 204,533 participants (7,199 with diabetes) in the sample.

2.2. Statistical analysis

The primary outcome measures were all-cause and cause-specific mortality (CVD, cancer, respiratory and 'other' causes). Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using logistic regression to explore the associations between diabetes and all-cause mortality; multinomial regression was utilised for the cause-specific mortality analyses. Unless otherwise indicated, all ORs are adjusted for age (grouped: 16–64, 65–74, 75+), sex, and smoking status (current smoker, ex-regular smoker, never smoked). BMI (grouped: <20 kg/m^2, 20–24.9 kg/m^2, 25–29.9 kg/m^2, ≥30 kg/m^2), CVD at baseline, demographic/socio-economic factors, and glycated haemoglobin were added to the model where indicated. Analyses were repeated first stratified by gender and secondly stratified by diagnosed CVD at baseline. Within all analyses the basic model refers to adjustment for age, sex and smoking, while the advanced model also includes BMI. The reference group for each analysis was those without diagnosed diabetes. All analyses were undertaken using SPSS V. 17 (SPSS Inc).

3. Results

3.1. Descriptive results

Seven thousand one hundred ninety-nine participants had diabetes (3.5%); 21,892 (10.7%) had CVD at baseline. Participants' mean age was 47 years (SD ± 19.2). Those with diabetes were considerably older (mean age 63 years (SD 15.1) than those without the disease (mean 47 years (SD 19.1)). The former also had a higher BMI (Table 1). Fifty-five percent of participants were female (48% among those with diabetes, 56% among those without). There were 20,051 deaths recorded, including 1,814 in those with doctor-diagnosed diabetes (25% of those with diabetes) and 18,237 among those without diabetes (9% of the non-diabetic sample). In terms of cause of death, 7,489 participants died of CVD; 5571 from cancer; 2,828 from respiratory disease; and 4,153 from other causes.