**Risk of selected eye diseases in people admitted to hospital
for hypertension or diabetes mellitus: record-linkage
studies**

Journal:	<i>British Journal of Ophthalmology</i>
Manuscript ID:	bjophthalmol-2012-301519.R1
Article Type:	Clinical science
Date Submitted by the Author:	n/a
Complete List of Authors:	Goldacre, Michael; University of Oxford, Unit of Health-Care Epidemiology Wotton, Clare; University of Oxford, Unit of Health-Care Epidemiology Keenan, Tiarnan; University of Manchester,
Keywords:	Epidemiology, Glaucoma, Retina

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Title

Risk of selected eye diseases in people admitted to hospital for hypertension or diabetes mellitus: record-linkage studies

Authors

Michael J. Goldacre, FFPHM¹, Clare J. Wotton, BSc¹, Tiarnan D. L. Keenan, MRCOphth^{2,3}

Institutions

1. Unit of Health-Care Epidemiology, Department of Public Health, University of Oxford, Oxford OX3 7LF, United Kingdom
2. Fight For Sight Clinical Fellow, University of Manchester, Manchester M13 9PT, United Kingdom
3. Manchester Royal Eye Hospital, Manchester M13 9WH, United Kingdom

Author for correspondence

Tiarnan D. L. Keenan
Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WH
Email: tiarnan.keenan@doctors.org.uk
Telephone: 01625584582. Facsimile: 01625582847

Keywords

Hypertension; diabetes mellitus; cataract; retinal artery occlusion; retinal vein occlusion; glaucoma; age-related macular degeneration; retinal detachment

Word count

2498

ABSTRACT

Aims

Associations between hypertension, diabetes mellitus, and some ophthalmic diseases are well established; associations with others are more speculative or equivocal. Our aim was to quantify associations accurately using large epidemiological datasets.

Methods

Analysis of the Oxford Record Linkage Study (ORLS), 1963-1998, and English national linked Hospital Episode Statistics (LHES), 1999-2010; calculation of rate ratios of eye disease in a hypertension cohort, and a diabetes cohort, compared with a reference cohort as control.

Results

The risk of cataract following hypertension was marginally elevated (rate ratio ORLS 1.15, 95% confidence interval 1.00-1.31; LHES 1.06, 1.01-1.10), as was risk of glaucoma and age-related macular degeneration (AMD) in the English population (glaucoma in LHES 1.07, 1.00-1.14; AMD in LHES 1.14, 1.02-1.27). Risk of retinal vein or artery occlusion was elevated 3-to-5 fold in both populations, while risk of retinal detachment was elevated in LHES at 1.52 (1.43-1.73). The risk of cataract in diabetes was high in both ORLS and LHES at, respectively, 2.95 (2.75-3.16) and 2.30 (2.24-2.35), as was risk of glaucoma at 2.47 (2.14-2.84) and 2.23 (2.15-2.30). Risks were high for AMD in both populations (10.3, 8.1-13.1, and 3.46, 3.35-3.58), and for retinal detachment (3.41, 2.71-4.25, and 7.96, 7.63-8.30). Risks were very high for retinal vein and artery occlusion.

Conclusions

With the exception of retinal vascular occlusion, elevations of risk of the ophthalmic diseases studied in hypertension were modest. By contrast, there were significant and substantial increases of risk for each eye disease in people with diabetes.

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INTRODUCTION

Known effects of systemic hypertension on the eye have been reviewed recently, along with associations with eye diseases which are more speculative^{1,2}. For example, systemic hypertension is known to increase the risk of some ophthalmic conditions such as retinal artery occlusion (RAO) and retinal vein occlusion (RVO), but it is less certain whether hypertension increases the risk of cataract or glaucoma and, if so, by what margin. Similarly, associations between diabetes mellitus and various ophthalmic conditions have been reviewed^{3,4}. Diabetes is known to increase the risk of cataract and RVO, but it is useful to quantify the scale of risk. An accurate assessment of the association between these systemic disorders and ophthalmic conditions is beneficial for several reasons: it enables the clinician to calculate the risk to an individual with hypertension or diabetes, which may guide primary and secondary prevention. It also guides the ophthalmologist towards appropriate investigations, on diagnosis of a particular eye condition. Finally, it may also reveal important insights into the pathogenesis of complex diseases, such as open angle glaucoma or age-related macular degeneration (AMD).

The purpose of this study was to determine whether analysis of routine hospital statistics can reliably identify known associations between hypertension or diabetes and eye diseases and, if so, to study and quantify associations where existing evidence is scarce or equivocal. We undertook record linkage studies of the risk of eye disease in people after admission to hospital with hypertension or diabetes, covering cataract, glaucoma, RAO, RVO, retinal detachment (RD) and AMD.

METHODS

Population and data

The Oxford record linkage study (ORLS)⁵ includes statistical abstracts of records of all hospital admissions (including day cases) in National Health Service (NHS) hospitals, and of all deaths in defined populations within the former Oxford NHS Region. The hospital data were collected routinely in the NHS as the region's hospital statistics system and were similar to English national Hospital Episode Statistics (HES). Death data derive from death certificates. The original ORLS covered the years 1963 to 1998. The ORLS dataset continued as a subset of English national

linked data (see below) and currently covers 1999-2010, but because of changes in data items available for linkage, the two datasets cannot be linked together. In this paper we analysed the original ORLS only. We also analysed the complete dataset of linked English national HES (1999-2010). The population covered by ORLS gradually expanded over time from an initial population of part of Oxfordshire (approximately 300 000 people) to all four counties of the former Oxford NHS region (population 2.5 million). The datasets used in this study (versions m6v2 for ORLS and v13 for England) have been constructed using software developed by staff in the ORLS team. The use of both the ORLS and national datasets, respectively covering 1963-1998 and 1999-2010, provides the opportunity to compare findings in two independent sources of data.

Record linkage for the historical ORLS file was undertaken as described elsewhere⁵ and that for the English national file was based on encrypted values of the NHS number (unique for each person registered with the NHS) and HESID number (a national number used for each person treated by an NHS hospital), and encrypted postcodes and dates of birth.

The basic methods were the same for the analysis of each disease and are described for hypertension and cataract. A hypertension cohort was constructed by identifying computerised records of all people with an admission or day case care for hypertension. The eligibility criteria were identification of each person's first recorded admission with hypertension, as the coded principal reason for hospital care, in an NHS hospital during the study period of 1963-1998 (ORLS) or 1999-2010 (England). A reference cohort was constructed by identifying the first admission for each individual with various other, mainly minor medical and surgical conditions (listed in Table 1 footnotes) in the ORLS or England dataset. This is based on a 'reference' group of conditions that has been used in other studies of associations between diseases⁶, using the standard epidemiological practice when using hospital controls of selecting a diverse range of conditions.

People were included in the hypertension or reference cohort if they did not have an admission for cataract either before or at the same time as the admission for hypertension or the reference condition. We searched the database for any subsequent

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NHS inpatient or day case care for cataract in these cohorts. We considered that rates of care for cataract in the reference cohort would approximate those in the general population of the region while allowing for migration in and out of it (data on migration of individuals were not available).

Statistical methods

We calculated rates of admission for cataract and the reference cohort conditions based on person-years, standardising the comparison between the hypertension and reference cohort by age, sex, year of admission and patients’ area of residence. The methods are described in detail in the Appendix. We calculated the rate ratio of cataract in the hypertension cohort relative to that in the reference cohort, its confidence interval and χ^2 statistics for its significance, as described elsewhere⁷.

We repeated the methods for the other eye diseases, as outcomes, and for the same diseases after a first recorded admission for diabetes mellitus.

RESULTS

Table 1 shows the number of people in each age group in the study who were admitted to hospital with hypertension or diabetes; it shows the percentage who were female; and it shows the matching ratio which is the number of people in each age group in the reference cohort who were matched to each person in the hypertension or diabetes cohort. We used all eligible records on the datafiles for the ‘controls’ in the reference cohorts. Matching ratios were considerably higher in the very young than the elderly but, because the analyses that follow are age standardised, the comparisons between the hypertension and diabetes cohorts, and the reference cohorts, are equivalenced in respect of age (in a stratified and standardised analysis of an existing dataset, no purpose is served by discarding control people to make a seemingly neat number of controls).

Hypertension

In people with hypertension, there was a numerically small, borderline significant, elevation of risk of cataract: the rate ratio, comparing the hypertension cohort with the

reference cohort, was 1.15 (95% confidence interval 1.00-1.31) in ORLS and 1.06 (1.01-1.10) in the national cohort (Table 2). The rate ratios for glaucoma were non-significant in the ORLS (0.89, 0.66-1.17) and borderline significant in the much larger English population (1.07, 1.00-1.14). These findings indicate that, if there is any real elevation of risk of cataract or glaucoma, it is very small in scale.

There was a four-fold elevation of risk of RAO (Table 2), significant in England though not significant in the very small numbers of the ORLS. There was a significant elevation of risk of RVO in both populations.

Hypertension was associated with an elevated risk of RD, significantly so in England (RR 1.52, 1.34-1.73) but not significant in ORLS (1.05, 0.60-1.72). Hypertension was also associated with a significant but modest elevation of risk of AMD in England (1.14, 1.02-1.27), and a similar level of risk without its attaining statistical significance in ORLS (1.27, 0.57-2.46).

Diabetes mellitus

Diabetes mellitus was associated with a clear, unequivocal elevation of risk of cataract, consistent in both populations (rate ratio in ORLS 2.95, 2.75-3.16; England 2.30, 2.24-2.35), and of glaucoma (ORLS 2.47, 2.14-2.84; England 2.23, 2.15-2.30): see Table 3. Risks of RAO and RVO were very high in both populations (Table 3), as were risks of RD (eg rate ratio 7.96, 7.63-7.80, in England) and AMD (3.46, 3.35-3.58 in England).

DISCUSSION

Main findings

Hypertension was strongly associated with RAO and RVO. Other associations were less obviously apparent. If there are real associations between hypertension and either cataract, glaucoma or AMD, their effect sizes are likely to be numerically modest. There was a significant association between hypertension and RD in the English national data but not ORLS data.

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Associations between diabetes and all eye conditions studied were strong, significant and unequivocal. There was a two to three-fold elevation of risk of cataract and glaucoma; and even higher risk elevations for retinal vascular occlusion, RD and AMD.

Comparison with literature – hypertension

Hypertension has been associated with cataract in some epidemiological studies⁸ but not others⁹. One prospective study found a significant relationship between incident cataract and systolic blood pressure (BP), but not with diastolic BP or hypertension¹⁰. In general, our results for cataract are in keeping with most studies in our finding of a small, borderline significant elevation in cataract risk. Pathophysiological mechanisms are not clear, and some have argued that potential associations may be explained partly by confounding factors such as smoking or diabetes¹⁰.

Similarly, hypertension has been associated with glaucoma in some population-based studies¹¹, while other prospective studies have failed to verify an association between incident glaucoma and systolic or diastolic BP¹². Potential mechanisms could include microvascular damage to the anterior optic nerve or posterior ciliary circulation, or an effect on intraocular pressure, but the situation is complicated by the relationship between systemic blood pressure, intraocular pressure and optic nerve perfusion pressure, as well as the use of antihypertensive medication¹³.

The association between hypertension and RAO is consistent with previous studies¹⁴. Retinal arterial occlusive disorders have been reviewed comprehensively¹⁵. One previous study demonstrated that the prevalence of hypertension in patients with central RAO was significantly higher than in an age-matched group¹⁴. Other studies have also shown an association between retinal arterial emboli (without occlusion) and hypertension; in one study¹⁶, after adjusting for age, the odds ratio for emboli in hypertension was 3.14 (95% CI 1.44-6.84).

Similarly, the strong association between hypertension and RVO is consistent with previous studies. In particular, a systematic review of 21 studies (comprising 2916 cases of any form of RVO, and 28 646 controls) generated a pooled odds ratio of 3.5 (95% CI 2.5-5.1)¹⁷.

Very few studies have reported an association between hypertension and RD. RD is most commonly rhegmatogenous, i.e. caused by break(s) in the neurosensory retina, usually through posterior vitreous detachment (PVD). Interestingly, one study examined the potential association between PVD and arterial hypertension, and reported no significant association¹⁸. However, it is possible that hypertension increases the risk of a retinal break causing RD by increasing delivery of fluid into the subretinal space. Another potential cause for our finding is that severe hypertension has been reported to lead to exudative RD¹⁹.

As regards AMD, our finding of a modest, borderline significant elevation in risk is consistent with the literature. A recent systematic review and meta-analysis examined 15 relevant studies, and combined odds ratio and/or relative risk outcomes by study design²⁰. The pooled estimates for three case-control studies demonstrated a significant association between hypertension and late AMD (odds ratio 1.48; 95% CI 1.22 - 1.78), though associations in the other studies were not statistically significant. Potential mechanisms linking hypertension and AMD are not clear, but may include damage to the choroidal circulation and Bruch's membrane.

Comparison with literature – diabetes mellitus

The association between diabetes and cataract has been reviewed recently²¹. Our findings of a relative risk of 3.0 (England) and 2.3 (ORLS) are consistent with previous reports: the Framingham Eye Study found a three-fold increase in cataract prevalence²², and other studies have documented associations with both prevalent and incident posterior subcapsular and cortical cataract²³. Potential pathophysiological mechanisms may involve the aldose reductase pathway, osmotic stress and advanced glycation end-products in the lens²¹.

Potential associations between diabetes and glaucoma remain controversial. A recent review²⁴ summarised 18 epidemiological studies examining the association between diabetes and open angle glaucoma; results varied widely, from several demonstrating no significant association, and other large studies reporting significant odds ratios of 1.68 and 2.12. Possible mechanisms may include neuronal injury through oxidative stress, microvascular damage and glial cell activation²⁴. In addition, our findings may

be explained in part by known associations between diabetes and neovascular glaucoma.

Few studies have reported on the relative risk of RAO in diabetes, which was very high in our study. As for hypertension, one previous study reported that the prevalence of diabetes in patients with central RAO was significantly higher than in an age-matched group¹⁴, though other authors have argued that there is no clear evidence that diabetic patients are at higher risk of RAO⁴.

The association between diabetes and RVO in our study is stronger than that found in previous studies, some of which reported no association¹⁷. A systematic review of 21 studies (described above) calculated a pooled odds ratio of 1.5 (95% CI 1.1-2.0), much lower than for hypertension¹⁸.

Few studies have reported on associations between diabetes and RD (all causes), which were strongly associated in our study. However, tractional RD is clearly linked to diabetes³. In addition, PVD occurs more commonly in diabetes²⁵, and may lead to increased risk of rhegmatogenous RD.

Diabetes and AMD were also strongly associated in our study. A systematic review and meta-analysis (described above) found a weak association between diabetes and late AMD (pooled relative risk 1.66; 95% CI 1.05-2.63) from four prospective cohort studies²⁰. However, pooled data from two cross-sectional studies and one case-control study showed no significant association. As for hypertension, potential mechanisms may involve damage to the choroidal circulation, Bruch's membrane and the retinal pigment epithelium.

Strengths and weaknesses

Strengths of the datasets include their size. The ORLS1 data provide long duration of follow-up; the English data provide a much larger and more recent population but with shorter follow-up. It was possible to study the risk of each of the eye disorders, and to compare risks of hypertension and diabetes, within the same populations and using the same study design. Thus each risk can be compared directly with the others.

The datasets have limitations. It seems likely that the levels of risk found are those at the more severe end of the spectrum of hypertensive and diabetic disease, because the datasets are limited to people who were admitted to hospital, or who received day case specialist care. We lack clinical, laboratory and treatment data. We have not attempted to distinguish between type 1 and type 2 diabetes (recording of type in routine administrative hospital statistics is unreliable). The cohorts are based on prevalent cases, the first record of hospital inpatient or day case care for each person with each condition, rather than being cohorts with follow-up from the date of first-ever diagnosis. Data are not available on patients who are treated in hospitals outside the area (this mainly affects the ORLS studies). The fact that there is unmeasured migration in the populations covered by the study, and the use of an internal reference cohort for comparison with the eye disorder rates in the cohorts with hypertension or diabetes, preclude meaningful calculation of absolute risks. We have also assumed that migration rates in the hypertension and diabetes cohorts are acceptably similar to those in the reference cohorts. Despite these limitations, the study identifies known associations very clearly, and there is therefore face validity that the findings are likely to be sound.

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APPENDIX

As above, we describe the method using the study of cataract following hypertension as the example. We took “date of entry” into each cohort as the date of first admission for hypertension, or reference condition, and “date of exit” as the date of first record of cataract, death, or the end of the data file (31st December 1998 for ORLS; 31st March 2010 for English national HES), whichever was the earliest. In addition, subjects in the reference cohort who, after inclusion, subsequently had an admission for hypertension (or, in the diabetes study, for diabetes) “exited” the reference cohort. They exited from the exact date of first admission for hypertension (or diabetes) and “entered” the hypertension (or diabetes) cohort from that date. In the ORLS cohort, in comparing cataract in the hypertension cohort with the reference cohort, we first calculated rates for cataract, stratified and then standardised by age (in five-year age groups), sex, calendar year of first recorded admission, and district of residence, to ensure that the results of group comparisons were equivalent in these respects. We used a similar approach to standardisation in the England dataset, stratifying by age (in five-year age groups), sex, calendar year of first recorded admission, region of residence, and quintile of patients’ Index of Deprivation score (as a measure of socio-economic status, which was not available in ORLS). We used the indirect method of standardisation, taking the combined hypertension and reference cohorts as the standard population. We applied the stratum-specific rates in the combined hypertension and reference cohorts to the number of people in each stratum in the hypertension cohort and then, separately, to those in the reference cohort. This gave us the expected number of people with cataract in the hypertension cohort (E^h) and in the reference cohort (E^r), to compare with the observed numbers in each cohort (O^h and O^r). We calculated the rate ratio of cataract in the hypertension cohort relative to that in the reference cohort using the formula (O^h/E^h) divided by (O^r/E^r). The confidence interval for the rate ratio and χ^2 statistics for its significance were calculated as described elsewhere⁷.

Acknowledgements

Over many years, the linked datafiles, and associated analytical software, were built by Leicester Gill, Myfanwy Griffith, Matt Davidson and David Yeates, Unit of Health-Care Epidemiology, University of Oxford.

Conflicts of interest

None (all authors)

Funding

The Unit of Health-Care Epidemiology is funded by the English National Institute for Health Research to analyse the linked data. The views expressed in this paper do not necessarily reflect those of the funding body.

TDLK is funded by Fight For Sight through a Clinical Fellowship.

Contributorship statement

MJG and CJW had the idea for the paper and performed data acquisition and analysis. MJG and TDLK interpreted the data, and wrote and revised the paper. MJG is guarantor.

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Ethical approval

Ethical approval for analysis of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

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TABLES

Table 1. Age and sex distribution of people admitted to hospital with hypertension or diabetes mellitus: number of people in each age stratum, percentage females, and matching ratio of numbers of cases in the reference cohort¹ per case in each age stratum with each exposure condition.

Age at admission to exposure cohort	ORLS1 (1963-1998)			England (1999-2010)		
	Number in exposure cohort (% of total)	Percentage of females	Matching ratio	Number in exposure cohort (% of total)	Percentage of females	Matching ratio
<i>Hypertension</i>						
0-29	394 (4.4)	47	665	4540 (5.3)	46	560
30-39	559 (6.2)	48	112	7157 (8.4)	40	128
40-49	1164 (12.9)	40	46	12400 (14.4)	40	66
50-59	1973 (21.9)	40	25	15408 (18.0)	43	47
60-69	2194 (24.4)	46	19	16329 (19.1)	49	35
70-79	1787 (19.8)	59	17	17219 (20.2)	56	22
80+	941 (10.4)	74	17	12526 (14.6)	65	17
Total	9012 (100)	49	57	85579 (100)	49	72
<i>Diabetes</i>						
0-29	4406 (23.6)	46	59	53915 (25.8)	45	47
30-39	1314 (7.0)	40	48	20356 (9.8)	35	46
40-49	1447 (7.8)	40	37	23650 (11.3)	34	37
50-59	2346 (12.6)	43	21	28765 (13.8)	32	31
60-69	3432 (18.4)	49	13	33695 (16.1)	42	25
70-79	3740 (20.1)	58	8	30625 (14.7)	48	23
80+	1961 (10.5)	68	7	17857 (8.5)	60	23
Total	18646 (100)	50	28	208863 (100)	43	35

¹ Conditions used in reference cohort, with Office of Population, Censuses and Surveys (OPCS) code edition 3 for operations and ICD10 code for diagnosis (with equivalent codes used for other coding editions): appendicectomy (OPCS3 441), hip replacement (810), knee replacement (820), squint (ICD10 H49-H51), otitis externa or media (H60, H65, H66), varicose veins (I83), haemorrhoids (I84), deflected septum, nasal polyp (J33+J34.2), impacted tooth and other disorders of teeth (K00-K03), inguinal hernia (K40), ingrowing toenail and other diseases of nail (L60), sebaceous cyst (L72.1), internal derangement of knee (M23), bunion (M20.1), selected fractures (S42, S52, S62, S82, S92) dislocations, sprains and strains (S03, S13, S23, S33, S43, S53, S63, S73, S83, S93), superficial injury and contusion (S00, S10, S20, S30, S40, S50, S60, S70, S80, S90).

Table 2. Hypertension followed by eye disorders: observed numbers of people with each eye disorder in the hypertension cohort, expected numbers with each eye disorder, rate ratios¹ and their 95% confidence intervals, and p-values.

Outcome: eye disorder	Population	Observed	Expected	Rate ratio	95% CI	p-value
Cataract	ORLS	237	208.0	1.15	1.00-1.31	0.04
	England	2220	2102.0	1.06	1.01-1.10	0.009
Glaucoma	ORLS	51	57.2	0.89	0.66-1.17	0.45
	England	949	888.0	1.07	1.00-1.14	0.04
Retinal artery occlusion	ORLS	2	0.5	4.67	0.51-21.00	0.14
	England	84	19.5	4.84	3.79-6.10	<0.001
Retinal vein occlusion	ORLS	4	0.8	5.62	1.41-16.50	0.002
	England	162	57.9	2.99	2.52-3.51	<0.001
Retinal detachment	ORLS	16	15.3	1.05	0.60-1.72	0.95
	England	242	161.0	1.52	1.34-1.73	<0.001
Macular degeneration	ORLS	9	7.2	1.27	0.57-2.46	0.61
	England	356	313	1.14	1.02-1.27	0.02

¹ Adjusted for sex, age in 5-year bands, time-period in single calendar years and district of residence in the ORLS datasets; and for sex, age in 5-year bands, time-period in single calendar years, region of residence and deprivation score associated with patients' area of residence, in quintiles, in the England dataset. The rate ratios are calculated as the ratio of the observed/expected number in the hypertension cohort to the observed/expected numbers in the reference cohort.

Table 3. Diabetes mellitus followed by eye disorders: observed numbers of people with each eye disorder in the diabetes cohort, expected numbers with each eye disorder, rate ratios and their 95% confidence intervals, and p-values.

Outcome: eye disorder	Population	Observed	Expected	Rate ratio	95% CI	p-value
Cataract	ORLS	944	354.0	2.95	2.75-3.16	<0.001
	England	7992	3642.0	2.30	2.24-2.35	<0.001
Glaucoma	ORLS	220	95.9	2.47	2.14-2.84	<0.001
	England	3547	1662.0	2.23	2.15-2.30	<0.001
Retinal artery occlusion	ORLS	8	0.6	24.50	8.23-71.60	<0.001
	England	388	55.2	9.31	8.26-10.50	<0.001
Retinal vein occlusion	ORLS	9	1.9	6.22	2.56-13.80	<0.001
	England	661	136.0	5.76	5.28-6.27	<0.001
Retinal detachment	ORLS	91	29.1	3.41	2.71-4.25	<0.001
	England	2769	432.0	7.96	7.63-8.30	<0.001
Macular degeneration	ORLS	115	17.3	10.3	8.10-13.10	<0.001
	England	4120	1287	3.46	3.35-3.58	<0.001

See footnotes to Table 2. In the Table 3 analysis, the rate ratios are calculated as the ratio of the observed/expected number in the diabetes cohort to the observed/expected numbers in the reference cohort.