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## **Incident ischaemic stroke and Type 2 diabetes: trends in incidence and case fatality in Scotland 2004–2013**

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## What's new?

- Using population-wide registers we describe contemporary trends in ischaemic stroke incidence and case fatality in people with and without a diagnosis of Type 2 diabetes.
- Declines in ischaemic stroke incidence and case fatality have occurred at the same rate in people with and without a diagnosis of Type 2 diabetes, despite attempts to intensify cardiovascular disease risk factor control in people with diabetes.
- Between 2004 and 2013, the prevalence of diagnosis of Type 2 diabetes in patients experiencing ischaemic stroke in Scotland increased from 13.5% to 20.3%.

## Abstract

**Aim** To describe trends in first ischaemic stroke incidence and case fatality in adults with and without a diagnosis of Type 2 diabetes prior to their ischaemic stroke event in Scotland between 2004 and 2013.

**Methods** Using population-wide hospital admission, death and diabetes datasets, we conducted a retrospective cohort study. Negative binomial and logistic regression models were used to calculate year-specific incidence and case-fatality rates for people with Type 2 diabetes and for people without diabetes.

**Results** During 41.0 million person-years of follow-up there were 69 757 ischaemic stroke events. Type 2 diabetes prevalence among patients who experienced ischaemic stroke increased from 13.5% to 20.3% between 2004 and 2013. Stroke incidence rates declined by 2.7% (95% CI 2.4, 3.0) annually for people with and without diabetes [diabetes/year interaction: rate ratio 0.99 (95% CI 0.98, 1.01)]. Type 2 diabetes was associated with an increased risk of ischaemic stroke in men [rate ratio 1.23 (95% CI 1.17, 1.30)] and women [rate ratio 1.41 (95% CI 1.35, 1.48)]. Case-fatality rates were 14.2%

and 12.7% in people with Type 2 diabetes and without diabetes, respectively. Case fatality declined by 3.5% (95% CI 2.7, 4.5) annually [diabetes/year interaction: odds ratio 1.01 (95% CI 0.98, 1.02)].

**Conclusions** Ischaemic stroke incidence declined no faster in people with a diagnosis of Type 2 diabetes than in people without diabetes. Increasing prevalence of Type 2 diabetes among stroke patients may mean that declines in case fatality over time will be less marked in the future.

## Introduction

Ageing populations, increasing obesity prevalence and improved survival have contributed to increasing Type 2 diabetes prevalence in developed countries [1]. Type 2 diabetes is an important cause of cardiovascular disease; ischaemic stroke, for example, is >1.5 times more common in people with diabetes than in similar populations without diabetes [2].

It is not known, however, whether recent improvements in the management and treatment of cardiovascular risk factors has reduced this excess risk of stroke in people with diabetes [3,4]. The overall incidence of ischaemic stroke is estimated to have declined by 13% in high-income countries between 1980 and 2010 [5], but it is unclear whether people with Type 2 diabetes have experienced similar benefits.

Scotland maintains a national register of all people with Type 2 diabetes, and this register is linked to population-based hospitalization and mortality registers. Using these large, robust population-wide databases, we have compared trends in ischaemic stroke incidence and case fatality in men and women with a diagnosis of Type 2 diabetes and in the population of people without diabetes in Scotland between 2004 and 2013.

## Methods

### Data sources

Mid-year population estimates by age, sex and decile of socio-economic status were obtained from the National Records of Scotland. Socio-economic status was defined using the 2012 version of the Scottish Index of Multiple Deprivation, an area-based measure of deprivation which uses information from seven domains, including income, employment, crime and education, to assign deprivation scores to 6505 small area-zones in Scotland (see <http://www.gov.scot/Topics/Statistics/SIMD> for further information).

Ischaemic stroke was defined as any hospital admission or death in which the primary diagnosis or cause of death was assigned a 10th revision of International Classification of Diseases (ICD-10) code of I63 and I64. Admission and death data were obtained from the National Records of Scotland death registrations and the national hospitalization register (Scottish Morbidity Record, SMR01), respectively. The SMR01 is a population-based register of hospital admission episodes occurring in Scotland, and holds information on patient conditions leading to admission. Unspecified strokes (ICD-10 I64) were included in the main analyses because the majority of these events are likely to be ischaemic stroke events, but sensitivity analyses were conducted in which unspecified strokes were excluded. A look-back period of 10 years was used to exclude previous stroke events, identified using the previously defined ICD-10 codes and the following ICD-9 codes: 433, 434 and 436. This look-back period is consistent with the definition of incident ischaemic stroke events in data published by the Information Services Division, Scotland. It ensures a consistent look-back period for all individuals, which is important because electronic records only go back to 1981 and lifetime data are not available. Case fatality was defined as a death within 30 days of a hospital admission with ischaemic stroke.

Type 2 diabetes status was ascertained by linkage to a research extract of the Scottish Care Information – Diabetes dataset. This national register collates demographic and clinical data from primary and secondary care clinics in Scotland. Since 2004, this register has covered >99.5% of people with a diagnosis of diabetes in Scotland. For research purposes, an algorithm, which uses clinician-recorded diagnosis, prescription data and age at diabetes diagnosis, was used to ascertain diabetes type. Presence of Type 2 diabetes was defined for the present study on the basis of a diagnosis of Type 2 diabetes prior to hospital admission or death from ischaemic stroke.

Approval for generation and analysis of the linked dataset was obtained from the Caldicott guardians of all health boards in Scotland, the Privacy Advisory Committee of the Information Services Division of NHS National Services Scotland and the national multi-centre research ethics committee.

### **Statistical analyses**

Analyses were conducted in people without a history of stroke, aged between 18 and 89 years, and who had available data on socio-economic status. The study group consisted of individuals with a diagnosis of Type 2 diabetes and a comparison group of individuals without a record of any type of diabetes prior to the ischaemic stroke event. To calculate the event numbers and person-time for people without diabetes, the number of incident stroke events and person-time at risk for the population of people with any type of diabetes were subtracted from the total number of events and person-time for the whole population (Fig. S1). The start and end dates were 1 January 2004 and 31 December 2013, respectively. Individual person-time was estimated as the number of days between study start date (or date of diabetes diagnosis if diagnosis occurred during the study period) until date of incident event, death or study end date.

Negative binomial regression models were used to estimate incidence rates and rate ratios by age, sex, calendar year, diabetes status and deprivation. Age in years was divided by 10 so that each increment was a decade. Deprivation decile 1 represented the most deprived group and deprivation

decile 10 represented the least deprived group. Calendar year was included in the models as a linear term. To investigate whether differential changes in ischaemic stroke risk had occurred in people with Type 2 diabetes and the comparison group, the final model included a two-way interaction term for calendar year and diabetes status. A three-way interaction term between sex, calendar year and diabetes status was also included to investigate whether the risk of ischaemic stroke was greater in women than in men with Type 2 diabetes and whether this relationship had changed over time. All other interaction terms between age, sex, deprivation, calendar year and deprivation were included if the exponentiated coefficient was  $\geq 1.05$  or  $\leq 0.95$ .

Logistic regression models were used to model case fatality by year, sex and diabetes status. For illustration, incidence and case fatality rates are presented for men and women aged 70 years in deprivation decile 5.

Statistical analyses were conducted in R, version 3.2.2

## Results

Overall, 69 757 ischaemic/unspecified stroke events occurred during 41.0 million person-years of follow-up. Of these events, 36 276 were coded specifically as ischaemic stroke. Among people with a pre-existing diagnosis of Type 2 diabetes there was a total of 11 437 ischaemic/unspecified stroke events during 1.9 million person-years. Table 1 shows the total number of ischaemic/unspecified stroke events by year, sex and diabetes status. Briefly, among patients who experienced ischaemic stroke, the proportion of people with Type 2 diabetes increased from 13.5% in 2004 to 20.3% in 2013. Overall, the proportion of people dying within 30 days of hospital admission declined from 13.8% to 10.7%. Crude case fatality was higher among people with Type 2 diabetes than in people without diabetes (14.2% vs 12.7%) and in women compared with men (14.9% vs 10.9%).

In models adjusted for age, sex and deprivation and diabetes, ischaemic/unspecified stroke incidence rates declined by 2.7% (95% CI 2.4, 3.0) each year overall. Rates of decline were similar in people with Type 2 diabetes to those without diabetes [rate ratio per year for interaction between diabetes and year 0.99 (95% CI 0.98, 1.01);  $P=0.91$ ]. Incidence rates were higher for men than women and in people with Type 2 diabetes than in people without diabetes (Fig.1). Overall, the rate ratios for the association between Type 2 diabetes and ischaemic/unspecified stroke risk for the whole study period were 1.41 (95% CI 1.35, 1.48) for women and 1.23 (95% CI 1.17, 1.30) for men. The rate ratios for the association between Type 2 diabetes and ischaemic stroke were 1.43 (95% CI 1.33, 1.53) and 1.42 (95% CI 1.33, 1.52) in women in 2004 and 2013, respectively. In men, the rate ratios were 1.28 (95% CI 1.20, 1.37) in 2004 and 1.21 (95% CI 1.13, 1.30) in 2013. Type 2 diabetes was associated with higher rate ratios in women than men (rate ratio for diabetes/sex interaction 1.15 (95% CI 1.09, 1.27);  $P <0.001$ ) and this effect did not change during the study period (rate ratio for diabetes/sex/year interaction 1.01 (95% CI 0.99, 1.02);  $P = 0.472$ ). After stratification by age, sex differences in risk of incident ischaemic stroke were most apparent in people aged <60 years (Fig. S2).

When ischaemic stroke deaths prior to hospital admission were excluded, Type 2 diabetes was associated with an increased risk of ischaemic stroke in men [rate ratio 1.26 (95% CI 1.20, 1.33)] and women [rate ratio 1.45 (95% CI 1.37, 1.52)].

Case fatality at 30 days declined in relative terms by 3.6% per year (95% CI 2.7, 4.5) in the study population and there was no significant difference in rates of decline by Type 2 diabetes status [diabetes/year interaction: odds ratio 1.01 (95% CI 0.98, 1.02);  $P= 0.58$  (Fig. 2)]. Case fatality was higher for people with Type 2 diabetes than in people without diabetes [age and deprivation adjusted odds ratio 1.18 (95% CI 1.09, 1.29) for women and 1.15 (95% CI 1.05, 1.26) for men].

## Sensitivity analyses

When unspecified stroke events (ICD-10 code I64;  $n=33\ 481$ , 48.0%) were excluded from the analyses, the findings were similar to the primary analyses (Table S1, Figs S3 and S4). Incidence rates of ischaemic stroke declined by 1.26% (95% CI 0.66, 1.87) per year in people with Type 2 diabetes and in people without diabetes [diabetes/year interaction: rate ratio 0.99 (95% CI 0.98, 1.01);  $P=0.91$ ]. Overall, Type 2 diabetes conferred a 40.5% (95% CI 31.2, 50.2) and 19.2% (95% CI 11.7, 27.3) excess risk of ischaemic stroke among women and men with Type 2 diabetes compared with people without diabetes.

## Discussion

Despite major initiatives to improve cardiovascular risk factors in people with Type 2 diabetes, ischaemic stroke incidence rates between 2004 and 2013 in people with a diagnosis of Type 2 diabetes in Scotland fell no faster than those in the general population [6,7]. This trend and the growing prevalence of Type 2 diabetes means that one-fifth of people who have an ischaemic stroke now have Type 2 diabetes, a trend which is likely to have important implications for reductions in ischaemic stroke case fatality in years to come.

As has been shown elsewhere, incidence rates of stroke in people with and without diabetes continued to decline between 2004 and 2013, reflecting improved treatment of hypertension and dyslipidaemia, as well as population-wide improvements in dietary salt intake and smoking prevalence [8,9]. Despite these improvements, Type 2 diabetes continues to confer an excess risk of ischaemic stroke, and this study indicates that the excess risk has remained unchanged.

In the present study, Type 2 diabetes was associated with a 45% and 26% increased risk of hospital admission for ischaemic stroke in women and men, respectively. This represents a considerably smaller excess risk than observed in previous studies [2,10]. For example, in one study based on data from England, Type 2 diabetes was associated with a 3.5-fold increased risk of hospital admission for

stroke between 2004 and 2009 [10]. The discrepancy in strength of association may be partly explained by the exclusion of stroke deaths which occurred prior to hospital admission from the analyses presented in the English study. These deaths accounted for 11.7% and 13.8% of stroke events in people with and without a diagnosis of diabetes respectively in our data. Few other studies have presented contemporary trends in the association between Type 2 diabetes and ischaemic stroke, and comparisons are difficult because of differences in definitions of stroke and diabetes. For example, in the USA, the relative risk of stroke associated with diabetes declined from 2.5 (95% CI 2.2, 2.7) in 2000 to 1.5 (95% CI 1.1, 2.0) in 2010, but this study did not distinguish between Type 1 and Type 2 diabetes, nor were estimates provided for stroke subtypes [3].

In an effort to improve health outcomes of people with chronic diseases such as Type 2 diabetes, the UK implemented the Quality and Outcomes Framework in 2004. This initiative incentivized general practices to reach a series of targets in the clinical management of chronic diseases and was expected to improve health outcomes for people with diabetes relative to the general population. Between 2004 and 2013, smoking prevalence declined and the management of hypertension, cholesterol and hyperglycaemia improved in people with Type 2 diabetes [11]. In addition it appears that diabetes may be being diagnosed earlier over time based on declining prevalence of retinopathy soon after diagnosis, perhaps as a result of wider diabetes screening [12]. While similar data for secular trends in cardiovascular disease risk factors in the Scottish population as a whole are limited, it is apparent that rates of obesity and hypertension have remained higher among people with Type 2 diabetes compared with the general population [13]. For example, 63% of the Scottish adult population were overweight or obese in 2014, compared with 87% of adults with Type 2 diabetes in 2014 [11,14]. Therefore, despite some improvements, people with Type 2 diabetes continue to have worse cardiovascular disease risk factor profiles than people without diabetes and subsequently remain at considerably greater risk of ischaemic stroke.

Consistent with previous findings, Type 2 diabetes had a greater relative influence on ischaemic stroke relative risk in women than men and this sex difference did not change considerably over time in the present study. A recent large meta-analysis reported a 27% higher relative risk of stroke for the effect of diabetes in women compared with men [15]; however, this relative risk ratio became only borderline significant after exclusion of haemorrhagic stroke [relative risk ratio 1.25 (95% CI 1.01–1.54)] and when studies in which baseline data were collected before 1985 were excluded [relative risk ratio 1.21 (95% CI 1.01, 1.46)]. Similar non-significant sex differences in risk of stroke were also observed in the Clinical Practice Research Datalink database and the General Practice Research Database in the UK [2,16]. In both studies the sex difference was more apparent among people aged <60 years, a finding that we have replicated here (Fig. S2).

Several explanations for the sex difference in diabetes-related excess risk of stroke have been proposed [17]. Firstly, while women in the general population usually have more favourable cardiovascular disease risk profiles than men, women exhibit greater deteriorations in cardiovascular disease risk profiles with the development of diabetes than men. For example, two UK-based studies have shown that men typically have lower BMI at diagnosis of Type 2 diabetes than women, suggesting that women need to gain more weight to develop diabetes than men, and this is particularly marked at younger ages of diagnosis [18,19]. Furthermore, several studies have shown that the relative difference in levels of cardiovascular disease risk factors, including levels of insulin resistance, lipids, fibrinogen and diastolic blood pressure between people with and without diabetes is greater in women than men [20–22].

Secondly, differences in diabetes management may also contribute to this sex difference, with some evidence to suggest that women with Type 2 diabetes are less likely than men to be prescribed statins, anti-hypertensive agents and β-blockers [17,23]. Similarly, in a cross-sectional study consisting of 10 191 people with Type 2 diabetes in Tayside, Scotland, women were less likely to have their cholesterol or blood pressure recorded than men [24].

Thirdly, poor glucose control may have a more adverse effect on women than men in terms of stroke risk [25].

Finally, even when treated similarly, women with Type 2 diabetes have been shown to be less likely to achieve cardiovascular disease risk factor targets than men [24,26–28]. In Scotland, women with diabetes were less likely to achieve all four targets for HbA<sub>1c</sub>, cholesterol, blood pressure and smoking cessation than men [odds ratio 0.75 (95% CI 0.67, 0.84)] [24]. Accordingly, women with Type 2 diabetes appear to have a greater cardiovascular risk factor burden compared with their counterparts without diabetes, emphasizing a greater requirement for more aggressive risk factor monitoring and treatment in women with diabetes.

Despite this sex difference in relative risks, fatal and non-fatal stroke events are more common in men than women after adjusting for age and deprivation, regardless of diabetes status.

Improvements in primary and secondary prevention in both men and women prior to and after diabetes diagnosis should therefore remain a priority.

Our findings of proportionately more patients with stroke having diabetes (now one in five at stroke presentation) are relevant to primary and secondary prevention of stroke. Notably, recent randomized controlled trials show that some of the newer diabetes therapies (e.g. the glucagon-like peptide-1 receptor agonist semaglutide, not yet licensed) may be associated with reduced stroke risk in people with diabetes [29], while pioglitazone may provide survival benefits post-stroke in patients with insulin resistance [30]. Further research is therefore required to determine to what extent more recent diabetes therapies can lower the risk of stroke or improve survival post-stroke.

The present study used population-based data to provide contemporary, long-term estimates which are representative of the entire Scottish population. Diabetes status was ascertained using the National Diabetes Register rather than through hospital admission databases which have been shown to under-report diabetes cases [31].

Unlike many previous studies which have been unable to distinguish between Type 1 and Type 2 diabetes, we were able to provide estimates for ischaemic stroke risk specifically for people with Type 2 diabetes. Significant differences in the aetiology, diagnosis and treatment of Type 1 and Type 2 diabetes are likely to contribute to considerable differences in stroke risk which would have been masked by combining these conditions. Furthermore, diabetes status is validated in the diabetes register using an algorithm which uses prescription and age at diagnosis data [32]. The risk of misclassifying Type 1 diabetes cases as Type 2 diabetes is therefore minimized.

The present study also has some limitations. There are likely to be inaccuracies in the coding of the event of interest because these are routinely recorded data. For example, a recent study identified that 25% of stroke events identified in the Scottish Stroke Care Audit were not recorded in the SMR01 dataset in 2010 [33]. Unidentified strokes in the SMR01 dataset are likely to have occurred through errors in the coding of primary diagnoses by coders and therefore, while this represents a significant proportion of stroke events, it seems unlikely that the recording of these events differed systematically by diabetes status.

The lack of availability of clinical data for the population of people without diabetes prevented any further analyses of differences in cardiovascular disease risk factors by diabetes status to explain the observed trends. Furthermore, the duration of diabetes is likely to be a relevant risk factor for stroke in people with diabetes, but this was not explored in the present analyses.

Finally, some people with diabetes that is first diagnosed during their stroke admission will have been included in the population without diabetes. This misclassification may have led to the underestimation of the strength of the association between Type 2 diabetes and ischaemic stroke, although it is uncertain whether this would also have affected whether the association between Type 2 diabetes and ischaemic stroke varied over time.

In conclusion, during the 10-year period between 2004 and 2013, stroke incidence declined regardless of diabetes status but risk of stroke remained 29–39% higher among people with a diagnosis of Type 2 diabetes than in the population of people without diabetes, despite significant efforts to improve cardiovascular disease risk factor management in people with Type 2 diabetes. The relative effect of Type 2 diabetes on stroke risk was higher in women but absolute risk was higher in men, indicating that primary and secondary prevention of both diabetes and ischaemic stroke are important in both sexes. Given the rising prevalence of diabetes in patients who experience stroke, further research investigating the effect of modern diabetes therapies on stroke incidence and case fatality are warranted.

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#### **Competing interests**

D.M. has received consultancy payments from Roche Pharmaceuticals and Galecto, and is a collaborator in a GSK-funded clinical trial. H.C. reports grants, personal fees and non-financial support from University of Edinburgh during the conduct of the study; grants and personal fees from Eli Lilly, grants from Astra-Zeneca, Boehringer Ingelheim, Pfizer and Novartis, outside the submitted work; and Stock ownership Roche and Bayer. R.S.L. has served on advisory boards for Novo Nordisk and Eli Lilly and has received travel grants from Novo Nordisk. R.J.M. has served on advisory boards for NovoNordisk, Eli Lilly and Sanofi Aventis. N.S. has served on advisory boards for Amgen, Sanofi, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Janssen and received grant support from AstraZeneca. S.H.W. received an honorarium from Global MedEd/Astra Zeneca. S.H.R., B.F., C.F., J.J.K., G.P.L., S.M. and S.P. have no disclosures.

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## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1** Rate ratios of incident ischaemic stroke (I63) in people with Type 2 diabetes compared to people without diabetes in Scotland between 2004 and 2013. Estimates adjusted for age, deprivation status and year/deprivation interaction

**Figure S1.** Three modes by which individuals contribute person-time to study. Participants were followed up until the first of ischaemic stroke event date, death or study end-point.

**Figure S2.** Rate ratios of incident ischaemic stroke (I63, I64) in people with Type 2 diabetes compared to people without diabetes in Scotland between 2004 and 2013, stratified by sex and age (60 years, >60 years). Estimates are presented for deprivation decile 5.

**Figure S3.** Incidence rates of ischaemic stroke after excluding unspecified stroke events per 100,000 for women and men with Type 2 diabetes and without diabetes between 2004 and 2013. The lines represent predicted incidence rates for men and women aged 70 years in deprivation decile 5.

**Figure S4.** Case fatality (%) following incident ischaemic stroke [excluding unspecified stroke events (I64)] for women and men with Type 2 diabetes and without diabetes between 2004 and 2013. The lines represent predicted case fatality for men and women aged 70 years and in deprivation decile 5.

**FIGURE 1** Incidence rates of ischaemic stroke (International Classification of Disease-10 codes: I63, I64) per 1000 person-years for (a) women and (b) men with Type 2 diabetes and without diabetes between 2004 and 2013. Lines represent predicted incidence rates for men and women aged 70 years and in deprivation decile 5. Model adjusted for the following interactions: sex/diabetes; sex/deprivation; deprivation/diabetes ( $P$  values all  $<0.001$ ).

**FIGURE 2** Case fatalities (%) after incident stroke for (a) women and (b) men with Type 2 diabetes and without diabetes between 2004 and 2013. Lines represent predicted case fatality for men and women aged 70 years and in deprivation decile 5.

**Table 1** Total number of stroke events (I63, I64), case fatality and person-time at risk for people aged 18–89 years, by diabetes status, sex and year in Scotland between 2004 and 2013

		Female						Male					
		Population without diabetes			Type 2 diabetes			Population without diabetes			Type 2 diabetes		
Year	Total events	Case fatalities (%)	Person-years,	Case fatalities (%)	Person-years,	Total events	Case fatalities (%)	Person-years,	Case fatalities (%)	Person-years,	Total events	Case fatalities (%)	Person-years,
		of hospital admissions)	1000	of hospital admissions)	1000		of hospital admissions)	1000	of hospital admissions)	1000		of hospital admissions)	
2004	3550	468 (16.0)	2016	505	73 (16.4)	65	3026	312 (11.8)	1804	525	45 (9.6)	76	
2005	3358	420 (14.8)	2026	516	79 (17.4)	70	2903	326 (12.6)	1815	564	74 (14.9)	82	
2006	3130	411 (15.5)	2034	507	75 (16.5)	75	2936	314 (12.1)	1827	509	59 (12.9)	88	
2007	2994	401 (15.8)	2046	485	75 (17.6)	79	2696	274 (11.4)	1842	535	68 (14.1)	94	
2008	3114	439 (16.5)	2056	499	83 (20.2)	82	2850	298 (11.7)	1855	586	78 (14.9)	99	
2009	3049	380 (14.4)	2064	567	90 (18.3)	87	2755	254 (10.1)	1865	622	60 (10.3)	105	

2010	2975	364 (13.9)	2075	577	77 (15.2)	90	2701	258 (10.5)	1877	610	64 (11.5)	111
2011	2856	338 (13.3)	2088	533	71 (15.3)	94	2673	210 (8.6)	1894	639	81 (13.8)	116
2012	2737	312 (13.0)	2092	620	85 (15.5)	97	2650	214 (8.7)	1896	668	73 (11.6)	121
2013	2737	310 (13.0)	2094	635	75 (13.4)	100	2630	198 (8.2)	1901	735	68 (10.0)	127
Total	30500	3843 (14.7)	20590	5444	783 (16.5)	838	27820	2658 (10.6)	18577	5993	670 (12.3)	1020







