ORIGINAL ARTICLE

Stroke among male professional drivers in Denmark, 1994–2003

F Tüchsen, H Hannerz, C Roepstorff, N Krause



Occup Environ Med 2006;63:456-460. doi: 10.1136/oem.2005.025718

Objectives: (1) To estimate the relative risk of stroke among various groups of professional drivers; (2) to determine if any excess risk should be attributed to infarction or haemorrhage; (3) to estimate the relative risk ratio for stroke among professional drivers living in Greater Copenhagen compared to those living outside the metropolis.

Methods: A cohort of 6285 bus drivers, 4204 car, taxi, and van drivers, and 25 879 heavy truck and lorry drivers were followed up for hospital admission due to stroke and sub-diagnoses in the period 1994-2003. Using hospital admission for all economically active men as the standard, the standardised hospitalisation ratios (SHR) were calculated, taking age and county into consideration.

See end of article for authors' affiliations

Correspondence to: Dr F Tüchsen, Department of Surveillance and Epidemiology, National Institute of Occupational Health, Lersø Parkallé 105, DK-2100 Copenhagen Ø, Denmark; ft@ami.dk

Accepted 7 April 2006 Published Online First 30 May 2006 **Results:** There was a high SHR for stroke among all groups of professional drivers (SHR = 132; 95% CI 121-141). Among car, taxi, and van drivers the SHR was 157 (95% CI 132-189), among bus drivers it was 139 (95% CI 119-163), and among heavy truck and lorry drivers it was 124 (95% CI 113-136). The excess risk for all groups of professional drivers was highest for cerebrovascular infarction (SHR = 139; 95% CI 124-155) and lowest for non-traumatic intracranial haemorrhage (SHR = 113; 95% CI 96-133). The excess risks for all groups were significantly higher for cerebrovascular infarction than for non-traumatic intracranial haemorrhage (relative risk ratio (RRR) 1.23; 95% CI 1.01-1.51). The RRR of stroke among drivers in the metropolitan area compared to rural areas was 1.13 (95% CI 0.94-1.36). The RRR for stroke among car, taxi, and van drivers compared to drivers of heavy trucks and of lorries was 1.28 (95% CI 1.03-1.57).

Conclusion: All groups of professional drivers are at increased risk of stroke. The excess risk is more due to cerebral infarctions than to non-traumatic intracranial haemorrhage. The risk of stroke is higher among drivers carrying passengers than among drivers carrying goods.

rofessional driving has been linked to ischaemic heart Disease (IHD) for about half a century,¹⁻¹³ but only three studies investigated stroke among professional drivers.⁵ ¹⁴ ¹⁵ The first of these studies¹⁴ with baseline measures in 1981 and follow up until 1990 reported a high relative risk ratio among city bus drivers compared to other bus drivers (RRR = 2.65; 95% CI 1.0-5.76). Another Danish study gave some indication⁸ that bus drivers on busy central lines in Copenhagen had a higher incidence of hospitalisation due to myocardial infarction than those working on other lines. The result was, however, not statistically significant. Since then the industry has been privatised so that the bus drivers who were civil servants had to accept a wage earner job status like their former colleagues working in smaller cities and in the countryside. The effective driving time was raised by approximately 25%. We therefore took a special interest in the risk of stroke among bus drivers living in Greater Copenhagen in this follow up study. The 1997 study¹⁴ also raised the question of whether a high relative risk found among drivers was due to infarction or haemorrhage. Since CT scanning was not common in the beginning of the 1980s, the question remained unanswered. Assuming the excess is due to infarctions, the risk factors causing stroke and IHD are more or less the same. Hannerz and Tüchsen found that drivers with passengers tend to have higher relative risks for circulatory diseases than drivers of vehicles carrying goods and they also found a significant excess risk of cerebrovascular disease (CVD).5 The follow up period was 1981-97 but the authors did not distinguish between cerebral infarction and intracranial haemorrhage.

Finkelstein *et al* suggest in a recent study¹⁵ that heavy equipment operators have an increased risk of IHD caused by

exposure to diesel fume. They also estimate the proportional mortality ratio for stroke but the results are not statistically significant.

A recent large scale intervention carried out in 2000 and 2001¹⁶ in the work environment of bus drivers is unlikely to have influenced the occupational health for the years reported here.

The aims of the present 10 year follow up study were: (1) to estimate the relative risk of stroke among various groups of male professional drivers; (2) to determine if any excess risk should be attributed to infarction or haemorrhage; and (3) to estimate the relative risk ratio for stroke among male professional drivers living in Greater Copenhagen compared to those living outside the metropolis.

METHODS

A cohort of 6285 bus drivers, 4204 car, taxi, and van drivers, and 25 879 heavy truck and lorry drivers were followed up in the period 1994–2003 for hospital admission due to stroke (I60–I64; ICD-10) non-traumatic intracranial haemorrhage (I60–I62), and cerebral infarction (I63) as the primary diagnoses (main cause of treatment). The ICD-10 code I64 covers stroke, not specified as haemorrhage or infarction. Since there were all together only 2009 women drivers in 2003, we have not analysed their stroke morbidity in detail.

All people in Denmark have a unique civil registration number. This number is very useful when information from different sources needs to be combined. The standard population (all economically active men) was identified in

Abbreviations: CVD, cerebrovascular disease; IHD, ischaemic heart disease; RRR, relative risk ratio; SHR, standard hospitalisation ratio the civil registration file for 1 January 1994. We excluded, however, people temporarily living abroad because they were less likely to be treated in Danish hospitals. The cohorts of drivers were established by means of the yearly register based census in 1993. People who, according to the national employment classification module had their main income as a driver during 1993, were admissible. The cohorts of drivers and the standard population were linked with the national patient register and followed up for first hospital admissions due to stroke in the period from 1 January 1994 to 31 December 2003.

Those who emigrated or died in the follow up were censored from the calculation of person-years at risk from the date they emigrated or died. People admitted to hospital due to stroke or stroke sub-diagnoses were censored from first day of admission.

Validity of the basic information

Age and gender are part of the civil registration number and therefore recorded almost without errors. The completeness and accuracy of the data were confirmed in the matching process where we had a 100% match of the files. One limitation of the present study is the exposure information, that is the register based classification of occupations. The classification is done annually by comparison of different sources such as registers from the mandatory labour market supplementary pension fund, mandatory reports from all companies with at least 10 employees who are obliged to classify their employees according to a Danish version of the international classification of occupation (DISCO88), and the national tax declaration register.

We used a representative national study, the Danish Work Environment Cohort Study (DWECS) to estimate the agreement of self reported versus employer reported occupations in 1995 and found an agreement of 45% on a four digit level.¹⁷ The agreement for three digits (all drivers) was 49%. Since DWECS is only a 0.25% sample, a considerable part of the disagreement is likely to be due to stochastic variation in DWECS. A random misclassification like this will bias the risk estimate slightly towards the mean as shown for the former classification of occupations where the agreement was 66%.¹⁸

Statistical methods

We used indirect standardisation to adjust for five year age groups. With regard to drivers in the entire country we used all economically active men in the total population of Denmark as standard population. With regard to drivers in Greater Copenhagen we used all economically active men in Greater Copenhagen as standard population. For drivers outside of Greater Copenhagen we used all economically active men outside of Greater Copenhagen as standard population.

RESULTS

Table 1 shows excess risks of stroke among all groups of professional drivers. The table also shows that this is mostly due to cerebral infarction and to a lesser degree due to nontraumatic intracranial haemorrhage.

The excess risk for all three groups of professional drivers was significantly higher for cerebrovascular infarction than for non-traumatic intracranial haemorrhage; the relative risk ratio being 1.23 (95% CI 1.01–1.51). The relative risk ratio for stroke among car, taxi, and van drivers compared to drivers of heavy trucks and lorries were 1.28 (95% CI 1.03–1.57) (table 1).

Table 2 compares relative risks for stroke of drivers in a metropolitan area with those in rural areas. Although table 2 does not contain any statistically significant results it may have some interest for researchers planning future studies. It has been suggested that bus drivers working on busy city lines have a higher risk of ischaemic heart disease.8 We would expect that this might be found also for cerebral infarction. However, table 2 shows, if anything, a consistent pattern of high relative risk ratios for non-traumatic intracranial haemorrhage and not for cerebral infarction. This may be due to the fact that the main risk factor for non-traumatic intracranial haemorrhage is an elevated systolic blood pressure, a condition that has been shown to be more prevalent in professional drivers. Fragile arterial vessels may rupture during an acute hypertensive period, while the development of artherosclerotic changes leading to cerebral infarction requires a prolonged exposure to hypertension and other risk factors and therefore is not immediately seen. In other words, the latency period for cerebral infarction may be

Table 1Age standardised hospitalisation ratios (SHR) 1994-2003 and 95% confidenceintervals (CI) among male bus drivers, heavy truck and lorry drivers, and car, taxi, andvan drivers due to non-traumatic intracranial haemorrhage, stroke, and cerebralinfarction

	No.	Cases	Expected	SHR	95% CI
Stroke (160-164)					
Car, taxi, and van drivers	4204	117	74.1	157	132-189
Bus drivers	6285	156	112.0	139	119-163
Heavy truck and lorry drivers	25879	453	365.8	124	113-136
All male drivers	36368	726	551.9	132	121-141
Non-traumatic intracranial haemorrhage (160–162)					
Car, taxi, and van drivers	4204	22	16.6	135	85-204
Bus drivers	6285	32	24.7	129	89-183
Heavy truck and lorry drivers	25879	90	86.1	105	84-129
All male drivers	36368	144	127.1	113	96-133
Cerebral infarction (163)					
Car, taxi, and van drivers	4204	51	31.1	164	122-216
Bus drivers	6285	64	47.0	136	105-174
Heavy truck and lorry drivers	25879	204	151.2	135	118-155
All male drivers	36368	319	229.3	139	124-155

Table 2 Relative risk ratios (RRR) and 95% confidence intervals (CI) due to stroke among male professional drivers living in Greater Copenhagen (GC) compared to those living outside GC

	Greater Copenhagen			Denmark outside GC				
	No.	Obs.	Exp.	No.	Obs.	Exp.	RRR	95% CI
Stroke (160-164)								
Car, taxi, and van drivers	1438	44	27.4	2941	73	48.7	1.07	0.72-1.58
Bus drivers	1539	36	26.3	4973	120	86.7	0.99	0.66-1.45
Heavy truck and lorry drivers	3180	62	43.7	23303	391	317.8	1.15	0.87-1.51
All male drivers	6157	142	97.4	31217	584	453.2	1.13	0.94–1.36
Non-traumatic intracranial haemori (160–162)	rhage							
Car, taxi, and van drivers	1438	11	6.0	2941	11	10.8	1.80	0.71-4.58
Bus drivers	1539	10	5.9	4973	22	19.0	1.47	0.62-3.22
Heavy truck and lorry drivers	3180	13	10.3	23303	77	74.7	1.23	0.62-2.22
All male drivers	6157	34	22.2	31217	110	104.5	1.45	0.96-2.15
Cerebral infarction (163)								
Car, taxi, and van drivers	1438	17	9.0	2941	34	21.7	1.21	0.63-2.22
Bus drivers	1539	7	8.6	4973	57	38.6	0.55	0.21-1.21
Heavy truck and lorry drivers	3180	14	14.0	23303	190	139.4	0.73	0.39-1.26
All male drivers	6157	38	31.6	31217	281	199.7	0.86	0.59-1.20

much longer and require longer than 10 year follow up periods to capture any associated risk of professional driving.

Altogether 2009 women were professional driver in 1993. In total 21 had a stroke during the 12 year follow up period against 17.8 expected (SHR = 118; 95% CI 77-181). There were 1205 female bus drivers (15 cases; SHR = 145; 95% CI 80-235).

DISCUSSION

We found a high risk of stroke especially due to cerebral infarction among professional drivers. The risk of stroke is higher among drivers carrying passengers than among drivers carrying goods, pointing to a possible role of customer stress. Our findings are in line with a former study showing a high risk of stroke among male professional drivers in the years 1981-90.14

It is strength of our study that it covers the entire working age population of Denmark and that the hospital system has a unified referral system. We used hospital admission as a proxy measure for the incidence of stroke and stroke subdiagnoses. Referral bias is often a major problem in studies using hospitalisations as the end point, especially in countries with a mix of public hospitals and expensive high class private hospitals. Hospital admission in Denmark is free of charge and there is a unified referral system. It was shown for ischaemic heart disease (IHD) that no occupational groups other than lower status hospital employees were admitted more often than expected when compared to mortality due to IHD.¹⁹ We therefore find it unlikely that our results should be attributed to referral bias. It is a weakness that we measure exposure only the year before follow up because exposure can change over time. This shortcoming tends to bias the result towards unity.

Several mechanisms for the association between driving and stroke have been proposed.

Psychosocial strain and hypertension

Malinauskiene found that truck drivers in Kaunas, Lithuania²⁰ had an odds ratio of 2.36 (95% CI 1.67–3.35) for myocardial infarction and one of the main risk factors was hypertension. Hypertension is also a major risk factor for stroke and several studies have reported elevated blood pressure levels among drivers.²¹⁻²³ Job stress may be a root cause for these findings. A recent study of 275 San Francisco urban transit operators (train and bus drivers) using a

composite regression model demonstrated that both observer based job barriers and self-reported intensity of job problems were independently and significantly associated with hypertension. Job barriers were defined as observable job stressors that required drivers to perform extra work or engage in risky behaviour to overcome a barrier (e.g. steering the vehicle into oncoming traffic in order to pass a double-parked car that has been a driving barrier; see Greiner *et al*²⁴ for details of the observer based job analysis). A former study of these drivers using self-reported job stress had failed to find an association with hypertension, probably because of the tendency of some individuals to use denial and repressive coping. Such coping seems to be most common in the group exposed to the most objectively measured stressors (job barriers and time pressure).25 It was suggested that observational methods are needed in addition to self-reported stressors to predict elevated blood pressure in urban transit operators. The job observations in San Francisco pointed to possibilities for both primary and secondary prevention, including better organisational and technical task design, increase of skill utilisation and decision authority,²⁵ and policy implications for urban planning.26 In Stockholm it was demonstrated that systolic blood pressure and heart rate at work, and perceived distress after work could be lowered by removing job hassles through traffic planning.27

Compliance with hypertension treatment has been difficult for drivers because of the diuretic effects of many antihypertensive medications and the lack of restroom access en route, resulting in higher rates of uncontrolled hypertension in this occupational group and thereby exacerbating the atherosclerotic effects of hypertensive disease.

We found that all groups of professional drivers are at increased risk of stroke and that the excess stems from cerebral infarctions rather than non-traumatic intracranial haemorrhage. It suggests that the high rate of stroke is caused by atherosclerotic changes, which in turn have been shown to be caused by hypertension and mental stress at work in the Kuopio Ischemic Heart Disease Risk Factor Study.²⁸ Wolf-Maier et al found a 60% higher prevalence of hypertension in Europe than in the USA and Canada.²⁹ They later³⁰ showed that hypertension in Europe remains untreated more often than in America. We do not know if it is also the case among professional drivers in Denmark, but if so, regular blood pressure screening at work may be an appropriate first step in reducing stroke in drivers. Many

Main messages

- All groups of professional drivers are at increased risk of stroke. The excess risk is due more to cerebral infarctions than to non-traumatic intracranial haemorrhage.
- The risk of stroke is higher among drivers carrying passengers than among drivers carrying goods.

Policy implications

- The study suggests that the high rate of stroke is caused by atherosclerotic changes, which in turn have been shown to be caused by hypertension and mental stress at work.
- Therefore a reduction of work stress and a limitation of driving hours should be considered, and hypertension monitored.

drivers work shift and night work which is assumed to be a risk factor for IHD,³¹ and recently also for the entire group of circulatory diseases.³²

Thread avoidance behaviour has been suggested as a risk factor for coronary heart disease among drivers, based on experimental studies with a driving task simulation and demonstrating that exposure to headlight glares overactivates the sympathetic autonomous nervous system, leading to diastolic blood pressure and heart rate increases, especially in drivers with hypertension or ischaemic heart disease.³³

Long working hours, obesity, and increased blood clotting factors

It has been known for half a century that drivers tend to be overweight,³⁴ an association between obesity, smoking, and working long hours has been reported,³⁵ and several studies have shown that obesity is a risk factor for stroke.^{36 37}

A new additional hypothesis could be derived from a recent study of Taiwanese taxi drivers.³⁸ Cross sectional measures showed that long driving time was positively associated with number of white blood cells, haematocrit, and number of platelets. These changes cause thickening of the blood and tend to increase in the likelihood of thrombosis. Long driving hours have also been predictive of an increased risk for neck and back injuries in a prospective study in San Francisco public transit operators.³⁹ Reduction of driving hours should be considered for prevention of both cardiovascular and musculoskeletal diseases observed among professional drivers.

In conclusion, all groups of professional drivers are at increased risk of stroke. The excess risk is due more to cerebral infarctions than to non-traumatic intracranial haemorrhage. The risk of stroke is higher among drivers carrying passengers than among drivers carrying goods.

Authors' affiliations

F Tüchsen, H Hannerz, C Roepstorff, National Institute of Occupational Health, Copenhagen Ø, Denmark

N Krause, Department of Medicine, University of California at San Francisco, USA

Funding: The National Institute of Occupational Health, Denmark, granted the study

Competing interests: none

REFERENCES

- Alfredsson L, Hammar N, Hogstedt C. Incidence of myocardial infarction and mortality from specific causes among bus drivers in Sweden. Int J Epidemiol 1993;22:57–61.
- 2 Belkic K, Emdad R, Theorell T. Occupational profile and cardiac risk: possible mechanisms and implications for professional drivers. Int J Occup Med Environ Health 1998;11:37–57.
- 3 Belkic K, Savic C, Theorell T, et al. Mechanisms of cardiac risk among professional drivers. Scand J Work Environ Health 1994;20:73–86.
- 4 Borgia P, Forastiere F, Rapiti E, et al. Mortality among taxi drivers in Rome: a cohort study. Am J Ind Med 1994;25:507–17.
- 5 Hannerz H, Tüchsen F. Hospitalizations among male drivers in Denmark. Occup Environ Med 2001;58:253–60.
- 6 Morris JN, Heady JA, Raffle PA, et al. Coronary heart-disease and physical activity of work. Lancet 1953;265:1053–7.
- 7 Hedberg GE, Jacobsson KA, Janlert U, et al. Risk indicators of ischaemic heart disease among male professional drivers in Sweden. Scand J Work Environ Health 1993;19:326–33.
- Netterstrøm B, Juel K. Impact of work-related and psychosocial factors on the development of ischemic heart disease among urban bus drivers in Denmark. Scand J Work Environ Health 1988;14:231–8.
- 9 Netterstrøm B, Suadicani P. Self-assessed job satisfaction and ischaemic heart disease mortality: a 10-year follow-up of urban bus drivers. Int J Epidemiol 1993;22:51–6.
- 10 Tüchsen F, Andersen O, Costa G, et al. Occupation and ischemic heart disease in the European Community. A comparative study of occupations at potential high risk. Am J Ind Med 1996;30:407–14.
- 11 Gustavsson P, Alfredsson L, Brunnberg H, et al. Myocardial infarction among male bus, taxi, and truck drivers in middle Sweden. Occup Environ Med 1996;53:235–40.
- 12 Tüchsen F, Endahl LA. Increasing inequality in ischaemic heart disease morbidity among employed men in Denmark 1981–1993: the need for a preventive policy. Int J Epidemiol 1999;28:640–4.
- 13 Bigert C, Gustavsson P, Hallquist J, et al. Myocardial infarction among professional drivers. Epidemiology 2003;14:333–9.
- 14 Tüchsen F. Stroke morbidity in professional drivers in Denmark 1981–1990. Int J Epidemiol 1997;26:989–94.
- 15 Finkelstein MM, Verma DK, Sahai D, et al. Ischemic heart disease mortality among heavy equipment operators. Am J Ind Med 2004;46:16–22.
- 16 Poulsen KB. The Healthy Bus project in Denmark: need for an action potential assessment. Health Promot Int 2004;19:205–13.
- 17 Tüchsen F, Hannerz H. Erhverv og hospitalsbehandlingsregistret. Kontrol af kvaliteten af oplysninger om fag og branche, 1993–2000 [The Occupational Hospitalisation Register. Control of quality of data regarding occupation and industry 1993–2000]. Copenhagen: Arbeidsmiljøinstituttet, 2004:1–42.
- industry 1993–2000J. Copenhagen: Arbeidsmiljøinstituttet, 2004:1-42.
 Bach E. Validering af EIR Et arbeidsepidemiologisk moniteringssystem. Copenhagen: Roskilde Universitetscenter, Arbeidsmiljøinstituttet, 1998.
- 19 Tüchsen F, Bach E, Marmot MG. Occupation and hospitalization with ischaemic heart diseases: a new nationwide surveillance system based on hospital admissions. Int J Epidemiol 1992;210:450–9.
- Malinauskiene V. Truck driving and risk of myocardial infarction. Przegl Lek 2003;60(suppl 6):89–90.
- 21 Albright CL, Winkleby MA, Ragland DR, et al. Job strain and prevalence of hypertension in a biracial population of urban bus drivers. Am J Public Health 1992;82:984–9.
- 22 Ragland DR, Winkleby MA, Schwalbe J, et al. Prevalence of hypertension in bus drivers. Int J Epidemiol 1987;16:208–14.
- 23 Winkleby MA, Ragland DR, Syme SL. Self-reported stressors and hypertension: evidence of an inverse association. Am J Epidemiol 1988;127:124–34.
- 24 Landsbergis P, Theorell T, Schwartz J, et al. Measurement of psychosocial workplace exposure variables. Occup Med 2000;15:163–88.
- 25 Greiner BA, Krause N, Ragland D, et al. Occupational stressors and hypertension: a multi-method study using observer-based job analysis and self-reports in urban transit operators. Soc Sci Med 2004;59:1081–94.
- 26 Ragland DR, Krause N, Greiner BA, et al. Studies of health outcomes in transit operators: policy implications of the current scientific database. J Occup Health Psychol 1998;3:172–87.
- 27 Rydstedt LW, Johansson G, Evans GW. The human side of the road: improving the working conditions of urban bus drivers. J Occup Health Psychol 1998;3:161–71.
- 28 Lynch J, Krause N, Kaplan GA, et al. Workplace demands, economic reward, and progression of carotid atherosclerosis. *Circulation* 1997;96:302–7.
- 29 Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003;289:2363–9.
- 30 Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 2004;43:10–17.
- 31 Beggild H, Knutsson A. Shift work and cardiovascular disease—evidence and risk factors: an overview. Scand J Work Environ Health 1998;25:85–99.
- 32 Tüchsen F, Hannerz H, Burr H. A 12-year prospective study of circulatory disease among Danish shift workers. Occup Environ Med 2006;63:451–5.
- 33 Belkic K, Ercegovac D, Savic C, et al. EEG arousal and cardiovascular reactivity in professional drivers: the glare pressor test. Eur Heart J 1992;13:304–9.
- 34 Heady JA, Morris JN, Raffle PA. Physique of London busmen; epidemiology of uniforms. Lancet 1956;271:569–70.

- 35 Emdad R, Belkic K, Theorell T, et al. What prevents professional drivers from following physicians' cardiologic advice? *Psychother Psychosom* 1998;67:226–40.
- Shinton R, Shipley M, Rose G. Overweight and stroke in the Whitehall study. J Epidemiol Community Health 1991;45:138–42.
- 37 Walker SP, Rimm EB, Ascherio A, et al. Body fat and fat distribution as predictors of stroke among US men. Am J Epidemiol 1996;144:1143–50.
- 38 Chen JC, Chen YJ, Chang WP, et al. Long driving time is associated with haematological markers of increased cardiovascular risk in taxi drivers. Occup Environ Med 2005;62:890–4.
- Krause N, Rugulies R, Ragland DR, et al. Physical workload, ergonomic problems, and incidence of low back injury: a 7.5-year prospective study of San Francisco transit operators. Am J Ind Med 2004;46:570–85.

OEM presents a new feature: Online First

In an innovative move, *OEM* is now publishing all original articles *Online First* within days of acceptance. These unedited articles are posted on the *OEM* website (www.occenvmed.com) weekly and are citable from the moment they are first posted; they are also deposited in PubMed. Every article will be published in print in its final, edited version when space in an issue becomes available. All versions will remain accessible via the website.

These articles can be accessed via the OEM homepage or by using standard author and keyword searches on OEM Online, Google, and PubMed.

Sign up for OEM announcements (www.occenvmed.com/cgi/alerts/etoc) to be notified when new papers are published Online First.