Hours of work and the risk of developing impaired fasting glucose or type 2 diabetes mellitus in Japanese male office workers

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Abstract

***Objective*—To investigate the association between duration of overtime and the development of impaired fasting glucose (IFG) or type 2 diabetes mellitus (DM).**

***Methods*—A cohort of 1266 Japanese male office workers aged 35–59 years and free of IFG (fasting plasma glucose concentration 6.1–6.9 mmol/l), type 2 DM (fasting plasma glucose concentration of 7.0 mmol/l or more or taking hypoglycaemic medication), history of diabetes, or medication for hypertension were re-examined over 5 successive years after their initial examinations in 1994.**

***Results*—138 men developed IFG or type 2 DM during the 5736 person-years of follow up. After controlling for potential predictors of diabetes, the relative risks of IFG or type 2 DM, compared with those who worked <8.0 hours a day, were 0.82 (95% confidence interval (95% CI) 0.54 to 1.26), 0.69 (95% CI 0.38 to 1.26), 0.63 (95% CI: 0.37 to 1.09), and 0.50 (95% CI: 0.25 to 0.98) for those who worked 8.0–8.9, 9.0–9.9, 10.0–10.9, and of 11.0 hours or more a day, respectively (p for trend=0.020). 87 and 54 men developed IFG and type 2 DM during the 5817 and 5937 person-years of follow up, respectively. The multivariate adjusted relative risks of IFG tended to decrease with an increase in hours of overtime work a day, but did not reach significance (p for trend=0.202). On the other hand, the multivariate adjusted relative risks of type 2 DM significantly decreased with an increase in hours of overtime work a day (p for trend=0.014).**

***Conclusion*—Longer overtime is a negative risk factor for the development of IFG or type 2 DM in Japanese male office workers.**

(*Occup Environ Med* 2001;**58**:569–574)

Keywords: long overtime; impaired fasting glucose; type 2 diabetes mellitus

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Accepted 30 April 2001

Type 2 diabetes mellitus (DM), which affects 7 million Japanese people over the age of 20 years,[1] is a complex disorder characterised by impaired secretion of insulin and increased resistance to insulin, and is associated with an increased risk of coronary heart disease, peripheral vascular disease, renal failure, and blindness.[2] Although age, obesity, and a family history of diabetes are well established risk factors for this condition,[3–5] evidence is increasing that type 2 DM shares common causal factors with cardiovascular disease and in particular with coronary heart disease. Previous studies have shown that alcohol intake, cigarette smoking, reduced physical activity, diets with a high glycaemic load and a low cereal fibre content, and psychological factors are associated with the risk of type 2 DM.[5–16] Furthermore, certain risk factors for coronary heart disease such as hypertension and dyslipidaemia are also known to be associated with the risk of type 2 DM.[17–20] As many of these factors are influenced not only by personal circumstances but also by work environments, it is reasonable to consider that working conditions are related to the development of type 2 DM.

The association between working conditions and the risk of type 2 DM has been reported showing that air traffic controllers who engaged in a high demand job had a higher prevalence of diabetes than other workers.[14] It was also reported that job strain and job stressors including a lack of worksite social support were associated with increased concentrations of glycosylated haemoglobin among non-diabetic populations.[15 16] Experimental studies in both animals and humans have also reported that psychological stress increases blood glucose and decreases insulin activity, which then could lead to glucose intolerance.[21 22] If it is assumed that long overtime is a major source of occupational stress, it is reasonable to expect an association between long overtime and the development of type 2 DM.

This study therefore prospectively examined the relation between duration of overtime and the development of impaired fasting glucose (IFG) or type 2 DM (as diagnosed with the new revised criteria of the American Diabetes Association (ADA) in 1997[23] for epidemiological studies) in normoglycaemic Japanese male office workers over a 5 year observation period.

Methods

STUDY COHORT

To evaluate the association between long overtime and the development of IFG or type 2 DM, a surveillance of the incidence of the two diseases was conducted between 1994 and 1999 among Japanese male office workers, not working in a shift system at T Corporation, one of the biggest building contractors in Osaka, Japan. All Japanese male office workers aged 35–59 in May 1994 were invited to attend a

survey (n=1581), and the participation rate was 99.9% (n=1580).

Of 1580 subjects, 269 (17.0%) were excluded because they had IFG, type 2 DM, a history of diabetes, or the use of antihypertensive medications at entry. Thus, the baseline population consisted of 1311 men. Also excluded were 45 men who did not participate in consecutive annual health examinations during the follow up period. The final study population for analysis consisted of 1266 men. Subjects who were identified as IFG or type 2 DM during repeat surveys up to May 1999 were defined as incidental cases of IFG or type 2 DM. Incident cases of IFG were followed up and considered to have type 2 DM if they reached that end point. Fourteen subjects who started medication for diabetes during the observation period were considered to be incident cases of type 2 DM. Owing to the age range of the study population, all cases of IFG or type 2 DM were diagnosed after the age of 35.

STUDY DESIGN

Fasting plasma glucose concentrations were measured at each annual health examination in May in the years 1994–9. The participants were asked to fast for at least 8 hours and to avoid smoking and heavy physical activity for more than 2 hours before the examinations. Fasting blood samples were drawn from an antecubital vein for the measurement of fasting plasma glucose concentration. Fasting plasma glucose concentrations were measured by the glucose dehydrogenase spectrophotometry method with an Olympus AU-5000 in 1994 and an Olympus AU-5200 in 1995–9 (Olympus Japan, Tokyo, Japan) by the FALCO biosystems Tokyo (Tokyo, Japan). Quality control of the laboratory was maintained internally, and the coefficients of variation between and within assays for plasma glucose were within 3% from 1994 to 1999. Normal fasting plasma glucose, IFG, and type 2 DM were assessed with the current guidelines of the ADA.[23] Normal fasting plasma glucose was defined as a fasting plasma glucose concentration <6.1 mmol/l. Impaired fasting glucose was defined as a fasting plasma glucose concentration of 6.1–6.9 mmol/l. Type 2 DM was defined as a fasting plasma glucose concentration 7.0 mmol/l or more or taking hypoglycaemic medication, because an oral glucose tolerance test was not performed in every subject.

STUDY ITEMS

The health examinations at entry included a medical history, a physical examination, anthropometric measurements, blood pressure measurements, biochemical measurements, and a questionnaire on job and health related behaviour. Additional details of the study items have been published elsewhere.[11 24] Medical history and the history of use of prescribed drugs were assessed for each subject by the examining physicians. Family history of diabetes was regarded as positive if one of the parents or siblings had diagnosed diabetes. Weight and height were measured in light clothing without shoes. Body mass index was calculated as weight (kg) divided by height (m) squared and was used as an index of overall adiposity. After a 5 minute rest in a quiet room, systolic blood pressure and diastolic blood pressure were measured on the right arm with a standard mercury sphygmomanometer. Biochemical measurements made by the Olympus AU-5000 included total cholesterol, high density lipoprotein cholesterol, and triglycerides. The job related variables occupation and position were each divided into two groups: architects or research workers and clerks for occupation; and managers and non-managers for position. Data on daily working hours were obtained by interview. Daily working hours for people holding a managerial position were not recorded by time clocks in this company. Therefore, we used subjectively reported working hours in this study. The participants were asked about their normal daily activities, including rising time, arrival at the company, going home times, and bedtimes. Hours of work each day were classified into five categories: working <8.0 hours a day, 8.0–8.9 hours a day, 9.0–9.9 hours a day, 10.0–10.9 hours a day, and 11.0 hours a day or more. The company's regular work hours were 8 hours a day (40 hours a week for 5 days a week). The questions queried health related behaviour—such as cigarette smoking, alcohol intake, eating breakfast, vegetable consumption, fruit consumption, and regular physical exercise. Health related behaviour was categorised into two groups: cigarette smoking (never smokers and ex-smokers *v* current smokers); alcohol intake (not consuming alcohol every day *v* consuming alcohol every day); eating breakfast (eating breakfast every morning *v* not eating breakfast every morning); vegetable consumption (eating vegetables every meal *v* not eating vegetables every meal); fruit consumption (eating fruit every day *v* not eating fruit every day); and physical exercise (exercising once a week or more *v* exercising less than once a week).

STATISTICAL ANALYSIS

The statistical differences of the characteristics at enrollment relative to hours of work a day were examined with the χ^2 test and one way analysis of variance (ANOVA). For each subject, person-years of follow up were counted from the date of enrollment to the date of the first incidence of IFG or type 2 DM or the date of follow up, whichever came first. Those who had been transferred to another locality or had retired during the follow up period have had their observation time censored as did those members of the cohort who were still in T Corporation, Osaka, at the end of follow up and who had no incidence of IFG or type 2 DM. The follow up rate was 95.6% of total potential person-years of follow up. Cox's proportional hazards models were used to evaluate the association between hours of work a day and the development of IFG or type 2 DM. Data were adjusted firstly for age alone, then for multiple covariates including age, occupation, position, body mass index, cigarette smoking, alcohol intake, eating breakfast,

*Table 1 Baseline characteristics of 1266 Japanese male office workers, by hours of work a day**

Characteristics	*Hours of work a day*					*p Value*
	<8.0 (n=358)	*8.0–8.9 (n=339)*	*9.0–9.9 (n=220)*	*10.0–10.9 (n=175)*	*≥11.0 (n=174)*	
Age (y)	48.5 (6.0)	47.6 (5.6)	46.1 (5.9)	44.4 (5.4)	44.3 (6.5)	<0.001
Occupation (%):						
Architect or research worker	49.4	64.9	57.7	67.4	69.5	<0.001
Position (%):						
Manager	61.5	60.5	56.8	47.4	45.4	<0.001
Body mass index (kg/m^2)	23.3 (2.6)	23.1 (2.6)	22.6 (2.6)	22.8 (2.5)	23.1 (2.6)	0.015
Cigarette smoking (%):						
Smoking cigarettes currently	52.8	51.9	45.0	51.4	52.9	0.406
Alcohol intake (%):						
Consuming alcohol every day	62.0	64.6	63.2	68.6	52.9	0.035
Eating breakfast (%):						
Not eating breakfast every morning	12.8	15.0	14.9	15.5	20.7	0.229
Vegetable consumption (%):						
Not eating vegetables every meal	52.8	47.2	43.6	50.3	52.9	0.190
Fruit consumption (%):						
Not eating fruit every day	72.3	70.2	70.9	68.0	80.5	0.082
Physical exercise (%):						
Exercising less than once a week	46.9	44.0	44.1	45.7	57.5	0.044
Family history of diabetes (%):	8.1	7.7	7.3	10.9	11.5	0.417
Systolic blood pressure (mm Hg)	129.1 (14.9)	129.0 (15.0)	128.8 (15.3)	125.0 (14.5)	125.6 (14.8)	0.004
Diastolic blood pressure (mm Hg)	77.7 (11.2)	77.1 (11.2)	77.8 (11.0)	75.1 (10.8)	75.6 (10.6)	0.029
Fasting plasma glucose (mmol/l)	5.05 (0.38)	5.07 (0.45)	5.05 (0.41)	5.01 (0.42)	4.99 (0.46)	0.277
Total cholesterol (mmol/l)	5.06 (0.82)	5.11 (0.85)	5.08 (0.82)	5.00 (0.72)	5.02 (0.82)	0.643
High density lipoprotein cholesterol (mmol/l)	1.38 (0.34)	1.39 (0.32)	1.38 (0.27)	1.43 (0.34)	1.38 (0.27)	0.335
Triglycerides (mmol/l)	1.59 (1.23)	1.51 (1.30)	1.36 (0.89)	1.35 (0.93)	1.37 (0.90)	0.031

*Unless otherwise indicated, values are expressed as the mean (SD).

vegetable consumption, fruit consumption, physical activity, family history of diabetes, systolic and diastolic blood pressure, fasting plasma glucose, total cholesterol, high density lipoprotein cholesterol, and triglycerides at entry. The linear trends in risks were evaluated by entering indicators for each category of exposure, and men who worked <8.0 hours a day were used as a reference category. In the statistical analyses, exact values were used for continuous variables, and dichotomised variables were coded as 1 for no potential risk factors and 2 for potential risk factors.

Data analysis was performed with the SPSS/PC statistical package (Marija J Norusis/SPSS, Chicago, IL, USA). All reported p values are two tailed and $p<0.05$ was considered to be significant.

Results

Table 1 shows the baseline characteristics of 1266 Japanese male office workers according to hours of work a day. Means of age, body mass index, systolic blood pressure, diastolic blood pressure, and triglycerides, and the percentages of those who were architects or research workers, managers, drank alcohol every day, and exercised less than once a week differed significantly among the five groups according to hours of work each day. Subjects who worked 10.0 hours or more a day were younger than those who worked <10.0 hours a day. The percentage of those who were architects or research workers tended to increase with an increase in hours of work a day. On the other hand, the percentage of those who were managers decreased with an increase in hours of work a day. Those who worked 9.0–10.9 hours a day had a lower body mass index. The percentage of those who drank alcohol every day was lowest and the percentage who exercised less than once a week was highest among those who worked 10.0 hours a day or more. Systolic and diastolic blood pressure were lower among those who worked 10.0 hours a day or more than among those who worked <10.0 hours a day. The concentration of triglycerides was lower among those who worked 9.0 hours a day or more than among those who worked <9.0 hours a day. The means of fasting plasma glucose, total cholesterol, and high density lipoprotein cholesterol, and the percentages of those who smoked cigarettes currently, did not eat breakfast every day, did not eat vegetables every meal, did not eat fruit every day, and had a family history of diabetes did not differ significantly among the five groups according to hours of work a day.

During the 5 year follow up period 138 men developed IFG or type 2 DM (5736 person-years, table 2). The multivariate adjusted relative risks of IFG or type 2 DM, compared with those who worked <8.0 hours a day, were 0.82 (95% confidence interval (95% CI) 0.54 to 1.26), 0.69 (95% CI 0.38 to 1.26), 0.63 (95% CI 0.37 to 1.09), and 0.50 (95% CI 0.25 to 0.98) for those who worked 8.0–8.9, 9.0–9.9, 10.0–10.9, and 11.0 hours or more a day, respectively. The test for trend across increasing categories of hours of work a day reached significance ($p=0.020$). Eighty seven men developed IFG during the 5 year follow up period (5817 person-years). The multivariate adjusted relative risks of IFG, compared with those who worked <8.0 hours a day, were 0.74 (95% CI 0.43 to 1.28), 0.77 (95% CI 0.37 to 1.62), 0.69 (95% CI 0.35 to 1.33), and 0.61 (95% CI 0.26 to 1.40) for those who worked 8.0–8.9, 9.0–9.9, 10.0–10.9, and 11.0 hours or more a day, respectively. The test for trend across increasing categories of hours of work a day did not reach significance ($p=0.202$). Fifty four men were diagnosed as having type 2 DM during the 5 year follow up period (5937 person-years). The multivariate adjusted relative risks of type 2 DM, compared with those

Table 2 Hours of work a day and the risks of impaired fasting glucose or type 2 diabetes among 1266 Japanese male office workers during 5 years of follow up

	Hours of work a day					*Test for trend p value*
	< 8.0	*8.0–8.9*	*9.0–9.9*	*10.0–10.9*	*≥11.0*	
Impaired fasting glucose or type 2 diabetes:						
Cases	47	43	20	16	12	
Person-years	1598	1516	1009	813	801	
Rate/1000 person-years	29.4	28.4	19.8	19.7	15.0	
Age adjusted relative risk	1.00	0.89	0.66	0.64	0.49	0.013
(95% CI)	(Reference)	(0.59 to 1.36)	(0.37 to 1.19)	(0.38 to 1.10)	(0.25 to 0.96)	
Multivariate adjusted relative risk*	1.00	0.82	0.69	0.63	0.50	0.020
(95% CI)	(Reference)	(0.54 to 1.26)	(0.38 to 1.26)	(0.37 to 1.09)	(0.25 to 0.98)	
Impaired fasting glucose:						
Cases	29	25	14	11	8	
Person-years	1631	1542	1015	822	808	
Rate/1000 person-years	17.8	16.2	13.8	13.4	9.9	
Age adjusted relative risk	1.00	0.86	0.78	0.76	0.57	0.167
(95% CI)	(Reference)	(0.50 to 1.47)	(0.38 to 1.60)	(0.40 to 1.46)	(0.25 to 1.28)	
Multivariate adjusted relative risk*	1.00	0.74	0.77	0.69	0.61	0.202
(95% CI)	(Reference)	(0.43 to 1.28)	(0.37 to 1.62)	(0.35 to 1.33)	(0.26 to 1.40)	
Type 2 diabetes:						
Cases	20	19	6	5	4	
Person-years	1651	1577	1048	838	824	
Rate/1000 person-years	12.1	12.0	5.7	6.0	4.9	
Age adjusted relative risk	1.00	0.91	0.46	0.43	0.36	0.014
(95% CI)	(Reference)	(0.48 to 1.72)	(0.17 to 1.26)	(0.17 to 1.10)	(0.12 to 1.11)	
Multivariate adjusted relative risk*	1.00	0.90	0.50	0.49	0.30	0.014
(95% CI)	(Reference)	(0.46 to 1.74)	(0.18 to 1.42)	(0.19 to 1.26)	(0.09 to 0.94)	

*Adjusted for age, occupation, position, body mass index, cigarette smoking, alcohol intake, eating breakfast, vegetable consumption, fruit consumption, regular physical exercise, family history of diabetes, systolic and diastolic blood pressures, fasting plasma glucose, total cholesterol, high density lipoprotein cholesterol, and triglycerides at entry.

who worked <8.0 hours a day, were 0.90 (95% CI 0.46 to 1.74), 0.50 (95% CI 0.18 to 1.42), 0.49 (95% CI 0.19 to 1.26), and 0.30 (95% CI 0.09 to 0.94) for those who worked 8.0–8.9, 9.0–9.9, 10.0–10.9, and 11.0 hours or more a day, respectively (p for trend=0.014).

Discussion

Although long overtime has received increasing attention for its adverse effects on health,[25] evidence linking long work hours to the risk of development of diabetes is very limited. To the best of our knowledge, only one longitudinal study in Japan[26] has reported that long overtime is a risk factor of type 2 DM among industrial male workers. In the present study, the risk of developing IFG or type 2 DM decreased in a dose-dependent manner with an increase in hours of overtime work a day among Japanese male office workers. This association remained significant after controlling for other covariates relevant to the development of IFG or type 2 DM—that is, age, occupation, position, obesity, smoking, alcohol drinking, eating breakfast, consumption of vegetables and fruit, regular physical activity, family history, blood pressure, fasting plasma glucose, and serum lipids. Furthermore, the relative risks of both IFG and type 2 DM tended to decrease with increasing categories of hours of work a day, and the negative association between hours of work a day and the risk of diabetes was more pronounced for the development of type 2 DM. These results suggest that long overtime is associated with a decreased risk of IFG or type 2 DM among Japanese male office workers.

The discrepancies found between a previous study in Japan[26] and our study might be derived from the different work environments and personal circumstances of these two populations. In the previous study,[26] the percentages of blue collar workers—such as mechanic or machine operators, and rotating shift labourers—were 69.7% and 46.3%, respectively. The percentages of those who had 13 years of education and were physically inactive (hardly any) were 14.5% and 37.0%, respectively. The means (SDs) for body mass index, alcohol consumption, and cigarettes smoked were 22.0 (2.4) kg/m^2, 15.9 (22.0) g of ethanol a day, and 12.9 (12.1) cigarettes a day, respectively. On the other hand, in our study, all the participants were white collar workers, not working in a shift system, and 60.3% of the participants were architects or research workers. The percentages of those who had 13 years of education and exercised less than once a week were 95.0% and 46.9%, respectively. Means (SDs) for body mass index, alcohol consumption, and cigarettes smoked were 23.2 (2.6) kg/m^2, 32.0 (25.4) g of ethanol a day, and 14.5 (16.6) cigarettes per day, respectively. Furthermore, the inconclusive results may have been influenced by different methods used to diagnose type 2 DM. In the previous study,[26] type 2 DM was diagnosed according to the World Health Organisation (WHO) criteria in 1980[27] by measuring the 75 g oral glucose tolerance test in people with both glucosuria and a fasting plasma glucose concentration 6.1 mmol/l or more. In our study, type 2 DM was defined with the newer ADA criteria in 1997.[23] As the influence of work environments is important for determining health related behaviour and psychological conditions,[25 26] there may be different associations between long overtime and the risk of IFG or type 2 DM among populations with different work circumstances. Further studies are needed to examine the effects of long overtime on IFG or type 2 DM in populations with different work circumstances using the standardised method to diagnose IFG or type 2 DM.

The contribution of long overtime to the lower risk of the development of IFG or type 2

DM is uncertain. In this population, to measure the physical activity of participants, their major physical activities were recorded every 15 minutes during an ordinary day and the 24 hour energy expenditure was calculated.[28 29] There were significant differences in mean (SD) ($p<0.001$, ANOVA) among the 24 hour energy expenditure values for the five subgroups of hours of work a day (2317 (284) kcal/day for <8.0 hours worked in a day, 2412 (292) for 8.0–9.9 hours, 2488 (293) for 9.0–9.9 hours, 2510 (258) for 10.0–10.9 hours, and 2611 (293) for 11.0 hours). Although this is of course unlikely to explain fully the decreased risk found in those who worked longer overtime, the negative association between hours of work each day and the development of IFG or type 2 DM might be derived from the high energy expenditure related to long working hours. However, those who worked 11.0 hours or more a day showed maladaptive lifestyle factors such as less frequent physical exercise and vegetable consumption in this study. As working long hours may influence many lifestyle factors related to IFG or type 2 DM, further research is needed to establish whether long overtime affects the development of IFG or type 2 DM independently.

There are several limitations to this study. One is that we assessed participants' working hours by their subjective reporting. However, because a questionnaire used in this study was confidential and data on daily working hours were only used for health management, over or underreporting their daily working hours is unlikely to have occurred.

The second limitation is that hours of work during the follow up were not included. Spearman's rank correlation coefficient was 0.586 ($p<0.001$) for hours of work a day between baseline and the end of follow up among 1056 subjects (83.4%) who could be followed up until the end of the study (May 1999). This indicates that those who worked longer overtime at entry tended to do so during the follow up period. The observed associations between hours of work a day at baseline and the decreased risk of the development of IFG or type 2 DM may reflect the effects of long working hours over a 5 year observation period. Furthermore, we did not assess participants' health related behaviour, blood pressure, and serum lipids during the follow up period. As obesity, alcohol intake, cigarette smoking, reduced physical activity, hypertension, and dyslipidaemia are known to be associated with the risk of type 2 DM,[3–11 17–20] health related behaviour, blood pressure, and serum lipids during the follow up period may also be associated with the risk of IFG or type 2 DM. Further research is needed to clarify the causal association between working hours and the risk of IFG or type 2 DM.

The third limitation is that in the present study, we could not evaluate job strain, job stressors, or social support at work.[14–16] However, the percentages of men with subjective symptoms—such as headache, ear noises, general fatigue, loss of appetite, loss of sleep, dizziness, constipation, fatigue of the eyes, and stiff shoulders—did not differ significantly among the five groups of hours of work a day. These results suggest that long overtime did not strongly affect subjective symptoms and might be unlikely to induce job stress in this population.

The final limitation is that the normoglycaemic cohort in this study, particularly in older age groups, may not be typical of the general population. The percentages of those who had IFG, type 2 DM, a history of diabetes, or medication for hypertension increased with age in this population. People whose plasma glucose concentration was already increased beyond the borderline, who had a history of diabetes, or who reported having taken drugs for hypertension during the initial examination were excluded from this survey. Thus, a healthy worker effect may exist in this study. Furthermore, as a cohort of this study is a restricted social class group of white collar workers, the results in this study could not be generalised to a national population.

Despite these potential limitations, our findings, obtained from a cohort of middle-aged Japanese male office workers, indicate that working longer overtime is negatively associated with the risk of the development of IFG or type 2 DM as diagnosed with the new criteria for epidemiological studies.

We thank all the employees and the Medical Office of the Osaka Main Office of Takenaka Corporation for their valuable cooperation for this study. We are also grateful to Ryuichi Kaneko and his colleagues at the Japan Labor and Welfare Association for collecting and coding the data accurately and consistently for 5 years. This study was supported in part by grant in aid for the prevention of lifestyle related diseases from the Arteriosclerosis Prevention Association, Tokyo, Japan.

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Vancouver style

All manuscripts submitted to *Occup Environ Med* should conform to the uniform requirements for manuscripts submitted to biomedical journals (known as the Vancouver style.)

Occup Environ Med, together with many other international biomedical journals, has agreed to accept articles prepared in accordance with the Vancouver style. The style (described in full in the *JAMA*[1]) is intended to standardise requirements for authors, and is the same as in this issue.

References should be numbered consecutively in the order in which they are first mentioned in the text by Arabic numerals on the line in square brackets on each occasion the reference is cited (Manson[1] confirmed other reports[2][3][4][5]). In future references to papers submitted to *Occup Environ Med* should include: the names of all authors if there are three or less or, if there are more, the first three followed by *et al*; the title of journal articles or book chapters; the titles of journals abbreviated according to the style of *Index Medicus*; and the first and final page numbers of the article or chapter. Titles not in *Index Medicus* should be given in full.

Examples of common forms of references are:

1 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomed journals. *JAMA* 1993;**269**:2282-6.
2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histmaine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med 1976*;**294**:687-90.
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Occup Environ Med 2001 58: 569-574
doi: 10.1136/oem.58.9.569