Schizophrenia, neuroleptic medication and mortality[†]

MATTI JOUKAMAA, MARKKU HELIÖVAARA, PAUL KNEKT, ARPO AROMAA, RAIMO RAITASALO and VILLE LEHTINEN

Background There is an excess of death from natural causes among people with schizophrenia.

Aims Schizophrenia and its treatment with neuroleptics were studied for their prediction of mortality in a representative population sample of 7217 Finns aged ⩾30 years.

Method A comprehensive health examination was carried out at baseline. Schizophrenia was determined using the Present State Examination and previous medical records.

Results During a 17-year follow-up, 39 of the 99 people with schizophrenia died. Adjusted for age and gender, the relative mortality risk between those with schizophrenia and others was 2.84 (95% CI 2.06–3.90), and was 2.25 (95% CI 1.61–3.15) after further adjusting for somatic diseases, blood pressure, cholesterol, body mass index, smoking, exercise, alcohol intake and education. The number of neuroleptics used at the time of the baseline survey showed a graded relation to mortality. Adjusted for age, gender, somatic diseases and other potential risk factors for premature death, the relative risk was 2.50 (95% CI 1.46–4.30) per increment of one neuroleptic.

Conclusions There is an urgent need to ascertain whether the high mortality in schizophrenia is attributable to the disorder itself or the antipsychotic medication.

Declaration of interest None.

[†]See invited commentary, p. 128, this issue.

Excess mortality among people with schizophrenia is partly a result of suicide (Brown, 1997; Harris & Barraclough, 1998; Heilä & Lönnqvist, 2003) but is also attributable to natural deaths (Brown, 1997; Mortensen, 2003), obviously explained by dietary and lifestyle factors (Brown, 1997) and possibly by use of neuroleptics (Montout *et al*, 2002; Ray & Meador, 2002). Most studies have included small and non-representative series of patients, short follow-up and no control for confounding factors. In a representative population sample over a long follow-up period, we found schizophrenia to be associated with excess mortality. In males this was owing to cardiovascular diseases (especially coronary disease), suicides and respiratory diseases and in females to cerebrovascular and respiratory diseases (Joukamaa *et al*, 2001). In the present study schizophrenia and its treatment with neuroleptic medication were studied for their prediction of mortality. We aimed to assess the effects of socio-demographic and lifestyle factors and somatic health on the mortality differentials.

METHOD

The current study was based on the Mini-Finland Health Survey (Aromaa *et al*, 1989). This comprehensive survey, carried out between 1978 and 1980, was designed to assess the health of adult Finns. The study population was a two-stage cluster sample drawn from the population register and stratified to represent Finns aged 30 years or over. The first stage comprised the selection of 40 representative areas. In the second stage a systematic sample of inhabitants was drawn from each area. The sample size was 8000 persons, of whom 7217 (90%) participated in the health examination (Aromaa *et al*, 1989).

The participants were first interviewed at home by local public health nurses and examined 1–6 weeks later by the Mobile Clinic of the Social Insurance Institution (SII) in two phases: a screening phase and a diagnostic (clinical) phase. The measurements of the screening phase, the methods used for studying chronic diseases and the basic results of the Mini-Finland Health Survey have been previously described in detail (Aromaa *et al*, 1989; Mäkelä *et al*, 1993). People with a disease history, symptoms or findings suggestive of chronic diseases were asked to participate in the diagnostic (clinical) phase, which was on average 3.5 months after the screening examination. Cardiovascular and respiratory diseases, diabetes and other somatic conditions were diagnosed on the basis of medical history, symptoms, physical examination and findings of the screening phase (Aromaa *et al*, 1989; Mäkelä *et al*, 1993).

Screening procedure

The methods used and the basic findings concerning mental disorders in the Mini-Finland Health Survey have been described in detail elsewhere (Lehtinen *et al*, 1990*a*,*b*). The screening for mental disorders comprised several parts. We tried to make the screen as sensitive as possible in order to minimise the number of false-negative cases, as no screen-negative people were invited to participate in the clinical phase of the study. The most important part of the screen was the 36-item version of the General Health Questionnaire (Goldberg, 1972). People were also invited to participate in the clinical phase if the records in the SII indicated that they were receiving a disability pension because of a mental disorder or were entitled to reimbursement for medication for such disorders (according to the National Health Insurance Scheme in Finland, all psychoses entitle the individual to free medication for their treatment). People were also selected if they reported having used health services (including those provided by a general practitioner) for a mental disorder or there was a self-perceived mental disorder. A total of 35% of those who participated in the screening phase were identified by various screening instruments; 95% of these agreed to participate in the clinical phase of the health examination.

Case-finding procedure

The most important method of psychiatric case identification in the clinical phase

was use of the short version of the ninth edition of the Present State Examination (PSE; Wing *et al*, 1974), which was administered by a psychiatric nurse. Training in the use of the PSE was provided by those who developed the method. The diagnoses were obtained via the computer program CATEGO–ID (Wing *et al*, 1978). Diagnostic information was also obtained from: case notes of participants in in-patient psychiatric care; SII records on disability pensions granted because of a mental disorder and on reimbursement for medication to treat psychoses; examination by the physician in the clinical phase of the survey; and assessment by the psychiatric nurse conducting the PSE interview. A panel of two psychiatrists reviewed the case notes of in-patients and the psychiatric records entitling individuals to SII benefits (disability pensions and reimbursement for medicines) to validate the diagnoses. For the final diagnostic assessments, a special computer program was designed that combined information from various sources, taking into account the degree of certainty and eliminating mutually incompatible assessment combinations. There were 99 people with a diagnosis of schizophrenia, giving an age-adjusted prevalence of 1.3% with no gender difference (Lehtinen *et al*, 1990*a*); this was in accordance with an earlier population study in Finland (Vaisanen, 1975).

The mortality of those examined has been systematically monitored since the baseline assessment. This information was obtained from the Central Statistical Office of Finland. The principal causes of death were coded according to ICD–8 (World Health Organization, 1974). During a follow-up from 1978 until 1994 the numbers of deaths (in parentheses deaths of people with schizophrenia) were as follows (see Joukamaa *et al*, 2001): a total of 1597 (39) deaths occurred; 876 (17) were caused by any cardiovascular disease; 130 (8) by respiratory diseases; 341 (7) by cancers; 72 (2) by injuries; and 20 (2) by suicides.

The definitions and measurement of lifestyle and related factors (level of education, exercise, smoking, alcohol intake, body mass index, systolic and diastolic blood pressure, serum total and high-density lipoprotein (HDL) cholesterol) have been described in more detail elsewhere (Aromaa *et al*, 1989; Mäkelä *et al*, 1993). Participants were asked about drugs prescribed by their physician. The use of neuroleptic drugs among people with schizophrenia was also recorded in the screening phase and was categorised according to the number prescribed. At the time of the baseline assessment the following conventional neuroleptics were the only neuroleptic drugs in use in Finland: phenothiazines with an aliphatic side-chain (promazine, chlorpromazine, levomepromazine); phenothiazines with a methylpiperazine side-chain (thioproperazine, trifluoperazine); phenothiazines with a piperazine-ethanol side-chain (perphenazine, fluphenazine, thiopropazate); phenothiazines with a piperidine side-chain (thioridazine, pericyazine, pipotiazine); thioxanthenes (chlorprothixene, clopenthixol, flupenthixol, thiothixene); butyrophenones (haloperidol, melperone, moperone); piperazines (pimozide); benzamides (sulpiride); and indoles (oxyperine).

A number of factors may be associated both with schizophrenia and mortality and could therefore confound the analysis. Age, gender, level of education, smoking, alcohol intake, exercise, body mass index, systolic and diastolic pressure, serum total and HDL cholesterol, diabetes, cardiovascular and respiratory diseases and other somatic diseases were therefore considered potential confounders or effect modifiers in the present study (Brown, 1997; Mortensen, 2003).

Statistical analysis

Logistic regression was used to estimate the associations between the potential confounding and effect-modifying factors and the prevalence of schizophrenia. The general linear model was used to compute multiple partial correlation ratios between those factors and the number of neuroleptic drugs among participants with schizophrenia. Cox's proportional hazards regression model (Cox, 1972) was used to estimate the strength of the association between schizophrenia and mortality and between neuroleptic drug use for schizophrenia and mortality. The number of neuroleptic drugs for schizophrenia was included both as a categorical variable and as a continuous variable in the model. Potential confounding and effect-modifying factors were entered into the Cox models. Adjusted relative risks and their 95% confidence intervals (CIs) were estimated based on this model. The SAS software package version 6.12 (SAS Institute, 1997) was used.

RESULTS

At baseline a number of lifestyle-related factors and chronic diseases were associated with the prevalence of schizophrenia. Since some of the associations seemed to differ between men and women, all these results were stratified according to gender (Tables 1 and 2). Heavy smoking and obesity were significantly associated with schizophrenia in both men and women, whereas being underweight proved to be a significant determinant only in men, and diabetes and other somatic diseases in women. Inverse associations with schizophrenia emerged for alcohol intake and serum HDL cholesterol in both men and women; in women there was an inverse association for exercise and in men for systolic pressure.

The age- and gender-adjusted relative risk of total mortality between people with schizophrenia and others was 2.84 (95% CI 2.06–3.90). The risk of mortality was increased among people with schizophrenia even after controlling for potential risk factors for premature death (low level of education, smoking, alcohol intake, exercise, body mass index, systolic and diastolic pressure, and total and HDL cholesterol) and coexistent somatic diseases (Table 3). As there was no difference between men and women in the association between schizophrenia and mortality, they were combined in these analyses.

There were only four unnatural deaths among those with schizophrenia. Adjusted for age and gender, the relative risk of natural death between people with schizophrenia and others was 2.80 (95% CI 2.00–3.93).

Of the 99 people with schizophrenia, 20 were taking no neuroleptic drug at baseline, 31 one drug, 34 two drugs and 14 three or more drugs. The most commonly used neuroleptic was thioridazine (34%), followed by perphenazine (20%), chlorpromazine (19%), levomepromazine (14%), chlorprothixene (13%) and haloperidol (12%); use of other neuroleptics was less than 10%. Among participants with schizophrenia, there was a strong inverse relationship between serum HDL cholesterol and the number of neuroleptic drugs prescribed (correlation coefficient$=-0.41$, $P<0.001$) that remained statistically significant after adjustment for age, gender, all lifestyle-related factors and coexistent somatic diseases (partial correlation$=-0.31$, $P=0.007$). Smoking was

Table I Relative risk for schizophrenia according to putative determinants of premature death and coexistent somatic diseases

Variable	Men				Women			
	n	Schizophrenia, *n*	RR	95% CI	*n*	Schizophrenia, *n*	RR	95% CI
Age, years								
30–44	1343	15	1.00[1]		1373	16	1.00[1]	
45–54	781	16	1.85	0.91–3.77	828	21	2.21	1.15–4.25
55–64	603	10	1.49	0.67–3.34	745	8	0.92	0.39–2.16
65–74	436	3	0.61	0.18–2.13	642	7	0.93	0.38–2.28
⩾75	159	2	1.13	0.26–5.0	307	1	0.28	0.04–2.10
Education								
Lower	2245	35	1.00		2660	41	1.00	
Average	692	8	0.72	0.33–1.59	814	10	0.71	0.34–1.46
Higher	385	3	0.48	0.15–1.60	421	2	0.26	0.06–1.11
Smoking								
Never	980	10	1.00		3029	38	1.00	
Quit	1136	9	0.75	0.30–1.87	369	4	0.86	0.30–2.44
Pipe, cigar or <20 cigarettes per day	677	14	2.04	0.90–4.62	385	5	1.03	0.40–2.67
⩾20 cigarettes per day	529	13	2.50	1.08–5.76	112	6	4.41	1.77–10.97
Alcohol intake								
None	915	27	1.00		2381	47	1.00	
1–99 g/week	1666	12	0.22	0.11–0.44	1414	6	0.17	0.07–0.40
100–249 g/week	237	1	0.12	0.02–0.91	48	0		
⩾250 g/week	504	6	0.35	0.14–0.86	52	0		
Body mass index (kg/m^2)								
<20.0	124	10	9.51	4.11–22.01	235	3	1.37	0.39–4.75
20.0–24.9	1346	15	1.00		1600	17	1.00	
25.0–29.9	1464	14	0.81	0.38–1.68	1351	12	0.85	0.40–1.82
30.0–34.9	351	5	1.19	0.43–3.32	558	12	2.24	1.03–4.85
⩾35.0	37	2	4.84	1.06–22.19	151	9	5.98	2.54–14.04
Exercise								
None	1085	19	1.00		1551	33	1.00	
Low level or occasional	1642	21	0.72	0.38–1.35	1835	18	0.42	0.23–0.76
High level and regular	591	5	0.47	0.17–1.28	503	2	0.16	0.04–0.69
Chronic diseases								
Cardiovascular								
No	2196	32	1.00		2628	34	1.00	
Yes	1126	14	0.82	0.42–1.62	1267	19	1.32	0.69–2.53
Respiratory								
No	2492	30	1.00		3488	49	1.00	
Yes	830	16	1.64	0.88–3.06	407	4	0.70	0.25–1.97
Diabetes								
No	3147	43	1.00		3658	44	1.00	
Yes	175	3	1.26	0.38–4.21	237	9	4.15	1.85–9.32
Other								
No	2570	33	1.00		2728	28	1.00	
Yes	752	13	1.36	0.70–2.64	1167	25	2.33	1.32–4.11

RR, relative risk.
1. Unadjusted.

also associated with the number of neuroleptics prescribed (correlation coefficient= 0.35, P=0.007), but the association did not reach statistical significance in the multifactorial analysis (partial correlation =0.27, P=0.14).

The number of neuroleptic drugs prescribed at the time of the baseline survey was related to the subsequent mortality. Of people with schizophrenia taking one, two and three or more neuroleptic drugs, 11 (35%), 15 (44%) and 8 (57%) respectively

Table 2 Odds ratio for schizophrenia according to blood pressure and cholesterol levels

Variable	Men				Women			
	Mean	s.d.	OR	95% CI[1]	Mean	s.d.	OR	95% CI[1]
Diastolic pressure, mmHg	88.6	11.8	0.82	0.61–1.11	86.1	11.7	1.22	0.92–1.60
Systolic pressure, mmHg	144.8	21.2	0.53	0.37–0.77	147.8	26.0	0.82	0.57–1.18
HDL cholesterol, mmol/l	1.59	0.4	0.70	0.50–0.98	1.79	0.4	0.47	0.34–0.65
Total cholesterol, mmol/l	6.9	1.3	1.04	0.78–1.39	7.0	1.4	1.17	0.88–1.55

OR, odds ratio; HDL, high-density lipoprotein.
1. Per an increment of 1 s.d.

Table 3 Relative risk of mortality in people with schizophrenia (n=99) compared with others (n=7118) after adjustment for potential confounding factors

Factors adjusted for	RR	95% CI
None (unadjusted)	2.01	1.46–2.76
Age, gender	2.84	2.06–3.90
Age, gender, level of education, systolic pressure, diastolic pressure, total and HDL cholesterol, body mass index, smoking, alcohol intake and exercise	2.21	1.58–3.08
Age, gender, cardiovascular disease, respiratory disease, diabetes and other somatic disease	2.89	2.10–3.98
All the factors and diseases above	2.25	1.61–3.15

RR, relative risk; HDL, high-density lipoprotein.

Table 4 Relative risk of mortality among people with schizophrenia (n=99) per an increment of one neuroleptic drug after adjustment for potential confounding factors

Factors adjusted for	RR	95% CI
None (unadjusted)	1.43	1.03–1.99
Age, gender	1.70	1.20–2.41
Age, gender, level of education, systolic pressure, diastolic pressure, total and HDL cholesterol, body mass index, smoking, alcohol intake and exercise	2.29	1.38–3.80
Age, gender, cardiovascular disease, respiratory disease, diabetes and other somatic disease	1.69	1.17–2.45
All the factors and diseases above	2.50	1.46–4.30

RR, relative risk; HDL, high-density lipoprotein.

died during follow-up, whereas the corresponding rate was 5 (20%) among those without neuroleptic medication. Table 4 shows the relative risk of dying among those with schizophrenia per increment of one neuroleptic drug adjusted for age, gender, lifestyle-related factors and chronic somatic diseases. Irrespective of the factors modelled, the relationship between number of neuroleptic drugs and mortality remained strong and statistically significant.

To assess the combined effect of schizophrenia and the number of neuroleptic drugs in the whole of the study population, the 68 people taking neuroleptics for other psychoses were excluded. Adjusted for age and gender, people with schizophrenia taking no neuroleptic, one, two and three or more neuroleptic drugs had relative risks (95% CI) of 1.29 (0.53–3.11), 2.97 (1.64–5.38), 3.21 (1.93–5.35) and 6.83 (3.40–13.71) respectively compared with those without schizophrenia or any antipsychotic treatment with neuroleptics. The association remained stable throughout the observation period. Even after excluding the first 10 years of follow-up, the corresponding estimates were 1.69 (0.42–6.80), 4.75 (1.95–11.53), 2.53 (0.63–10.21) and 5.35 (1.33–21.55).

DISCUSSION

Main findings

The present study demonstrated a graded relationship between the number of neuroleptic drugs prescribed and mortality of those with schizophrenia. This relationship and the excess mortality among people with schizophrenia could not be explained by coexistent somatic diseases or other known risk factors for premature death. To our knowledge this was the first study to analyse such associations in the general population using a prospective design.

Although the excess mortality of people with schizophrenia was first demonstrated before the Second World War, the causes have varied over the years, especially before the neuroleptic era (see Brown, 1997). It has been claimed that the contemporary high natural mortality in schizophrenia results from a variety of lifestyle factors (Brown, 1997; Mortensen, 2003). Of these factors we were able to consider several (smoking, exercise, body mass index, blood pressure, serum total and HDL cholesterol), but not all (e.g. dietary factors). However, after adjustment for these factors the excess mortality of people with schizophrenia persisted. Similarly, comorbid somatic diseases did not account for the mortality. Obviously there are other factors associated with mortality in schizophrenia and the association with neuroleptic drugs was very clear. This remained after adjustment for many different potentially confounding factors. At the time of the baseline survey only classic neuroleptic drugs were in use in Finland.

It is now well known that most or all classic neuroleptics can cause prolongation of the QT interval of the electrocardiogram

which is associated with the potentially fatal arrhythmia torsade de pointes (Witchel *et al*, 2003). Recently, in a large study Ray *et al* (2001) showed that prescription of moderate doses of antipsychotics was associated with large relative and absolute increases in the risk of sudden cardiac death. It has been proposed that antipsychotic drugs might also be associated with venous thrombosis, pulmonary embolism (Thomassen *et al*, 2001) and asthma mortality (Joseph *et al*, 1996). These associations could explain at least some of the deaths from respiratory diseases in the present study.

Neuroleptic polypharmacy

The risk of dying increased in our study if the participants were taking more than one neuroleptic drug. This is in line with previous findings. Waddington *et al* (1998) found that receiving more than one antipsychotic concurrently was associated with reduced survival in a 10-year follow-up of 88 people with schizophrenia. In a French study the mortality among patients with chronic schizophrenia was associated with the dosage of neuroleptics (Bralet *et al*, 2000). Why is more than one neuroleptic drug prescribed? We can presume that one reason might be the lack of response to a single antipsychotic, possibly related to the severity of the illness. Is it also possible that the most severe forms of schizophrenia carry a higher risk of dying than less severe schizophrenia. However, it must be borne in mind that antipsychotic polypharmacy can also lead to increased side-effects because of the potential influence on many receptors in addition to brain D_2 dopamine receptors (Waddington *et al*, 1998).

If classic neuroleptics were the cause of premature deaths among people with schizophrenia it could be assumed that the excess mortality would have decreased with the introduction of the newer atypical antipsychotics. However, a Swedish study found an increase in mortality in patients with schizophrenia (Osby *et al*, 2000). The newer atypical antipsychotic agents can affect somatic health in different ways (Wirshing *et al*, 2003).

Study strengths and limitations

The strengths of the present study included a long follow-up and a representative sample with a high participation rate. Because of the comprehensive nature of the Mini-Finland Health Survey we were able to take many potential confounding factors into account. The main screening instrument used, the General Health Questionnaire, is most suitable for screening for non-psychotic psychiatric illnesses such as anxiety and mood disorders. However, other aspects of our screening procedure, especially review of the SII records concerning disability pensions and reimbursement for medicines used to treat severe mental disorders, identified those with psychotic disorders. Another limitation was that we were not able to define the total period of neuroleptic use or total dosage or to assess the impact of prior treatment. In addition, the number of people with schizophrenia was relatively low, only 99, of whom 39 died during follow-up. In spite of these limitations we consider the results valid. The association of the use of neuroleptic drugs and mortality poses questions which could not be answered in this study. A careful quantitative analysis of the association of neuroleptic drug dosage and mortality would be especially interesting.

CLINICAL IMPLICATIONS

- The somatic health of people with schizophrenia is an important issue.
- The use of classical neuroleptic drugs is associated with mortality in schizophrenia.
- A combination of neuroleptic drugs seems to increase the risk of mortality.

LIMITATIONS

- The statistical power of the present study was insufficient for subgroup analyses.
- Since the baseline assessment was completed in the 1970s, it was not possible to use standardised criteria for schizophrenia.
- We were not able to analyse the total period of neuroleptic use and the total dosage.

MATTI JOUKAMAA, MD, PhD, Tampere School of Public Health, University of Tampere and Department of Psychiatry, Tampere University Hospital, Tampere; MARKKU HELIÖVAARA, MD, PhD, PAUL KNEKT, PhD, ARPO AROMAA, MD, PhD, National Public Health Institute, Helsinki; RAIMO RAITASALO, PhD, Social Insurance Institution, Helsinki; VILLE LEHTINEN, MD, PhD, National Research and Development Centre for Welfare and Health, Helsinki, Finland

Correspondence: Dr Matti Joukamaa, Department of Social Psychiatry, Tampere School of Public Health, University of Tampere, FIN-33014, Finland. E-mail: matti.joukamaa@uta.fi

(First received 28 October 2004, final revision 15 March 2005, accepted 18 May 2005)

Conclusions

More attention should be paid to the somatic health of people with schizophrenia. Our results indicate a need to modify the deleterious lifestyle factors of patients with schizophrenia previously recommended by Brown *et al* (2000). The recognition and medical management of somatic diseases among people with schizophrenia is a challenge to psychiatrists. Future research needs to determine whether the high mortality among those with schizophrenia is mainly attributable to the disorder per se or to the antipsychotic medication. Study of the association between the newer antipsychotic drugs and mortality in patients with schizophrenia will be important after a sufficient period of treatment has elapsed to allow long-term follow-up.

REFERENCES

Aromaa, A., Heliövaara, M., Impivaara, O., *et al* (1989) Aims, methods and study population. Part I. In *The Execution of the Mini-Finland Health Survey* (eds A. Aromaa, M. Heliövaara, O. Impivaara, *et al*). Publication no. ML:88. Helsinki: Social Insurance Institution.

Bralet, M. C., Yon, V., Loas, G., *et al* (2000) Causes de la mortalité chez les schizophrènes: étude prospective sur 8 ans d'une cohorte de 150 schizophrènes chroniques. *Encéphale*, **26**, 32–41.

Brown, S. (1997) Excess mortality of schizophrenia. A meta-analysis. *British Journal of Psychiatry*, **171**, 502–508.

Brown, S., Inskip, H. & Barraclough, B. (2000) Causes of the excess mortality of schizophrenia. *British Journal of Psychiatry*, **177**, 212–217.

Cox, D. R. (1972) Regression models and life-tables. *Journal of the Royal Statistical Society B*, **34**, 187–220.

Goldberg, D. P. (1972) *The Detection of Psychiatric Illness by Questionnaire*. Maudsley Monograph 21. London: Oxford University Press.

Harris, E. C. & Barraclough, B. (1998) Excess mortality of mental disorder. *British Journal of Psychiatry*, **173**, 11–53.

Heilä, H. & Lönnqvist, J. (2003) The clinical epidemiology of suicide in schizophrenia. In *The Epidemiology of Schizophrenia* (eds R. Murray, P. Jones, E. Susser, *et al*), pp. 288–316. Cambridge: Cambridge University Press.

Joseph, K. S., Blais, L., Ernst, P., *et al* (1996) Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ*, **31**, 79–82.

Joukamaa, M., Heliövaara, M., Knekt, P., *et al* (2001) Mental disorders and cause-specific mortality. *British Journal of Psychiatry*, **179**, 498–502.

Lehtinen, V., Joukamaa, M., Jyrkinen, E., *et al* (1990*a*) Prevalence of mental disorders among adults in Finland. Basic results from the Mini-Finland Health Survey. *Acta Psychiatrica Scandinavica*, **81**, 418–425.

Lehtinen, V., Joukamaa, M., Jyrkinen, E., *et al* (1990*b*) Need for mental health services of the adult population in Finland: results from the Mini-Finland Health Survey. *Acta Psychiatrica Scandinavica*, **81**, 426–431.

Mäkelä, M., Heliövaara, M., Sievers, K., *et al* (1993) Musculoskeletal disorders as determinants of disability in Finns aged 30 years or more. *Journal of Clinical Epidemiology*, **46**, 549–559.

Montout, C., Casadebaig, F., Lagnaoui, R., *et al* (2002) Neuroleptics and mortality in schizophrenia: prospective analysis of deaths in a French cohort of schizophrenic patients. *Schizophrenia Research*, **57**, 147–156.

Mortensen, P. B. (2003) Mortality and physical illness in schizophrenia. In *The Epidemiology of Schizophrenia* (eds R. Murray, P. Jones, E. Susser, *et al*), pp. 275–287. Cambridge: Cambridge University Press.

Osby, U., Correia, N., Brandt, L., *et al* (2000) Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophrenia Research*, **45**, 21–28.

Ray, W. A. & Meador, K. G. (2002) Antipsychotics and sudden death: is thioridazine the only bad actor? *British Journal of Psychiatry*, **180**, 483–484.

Ray, W. A., Meredith, S., Thapa, P. B., *et al* (2001) Antipsychotics and the risk of sudden cardiac death. *Archives of General Psychiatry*, **58**, 1161–1167.

SAS Institute (1997) *SAS/STAT Software: Changes and Enhancements through Release 6.12*. Cary, NC: SAS Institute.

Thomassen, R., Vandenbroucke, J. P. & Rosendaal, F. R. (2001) Antipsychotic medication and venous thrombosis. *British Journal of Psychiatry*, **179**, 63–66.

Vaisanen, E. (1975) Psychiatric disorders in Finland. *Acta Psychiatrica Scandinavica Supplementum*, **263**, 22–33.

Waddington, J. L., Youssef, H. A. & Kinsella, A. (1998) Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *British Journal of Psychiatry*, **173**, 325–329.

Wing, J. K., Cooper, J. E. & Sartorius, N. (1974) *The Measurement and Classification of Psychiatric Symptoms*. London: Cambridge University Press.

Wing, J. K., Mann, S. A., Leff, J. P., *et al* (1978) The concept of a case in psychiatric population surveys. *Psychological Medicine*, **8**, 203–217.

Wirshing, D. A., Pierre, J. M., Erhart, S. M., *et al* (2003) Understanding the new and evolving profile of adverse drug effects in schizophrenia. *Psychiatric Clinics of North America*, **26**, 165–190.

Witchel, H. J., Hancox, J. C. & Nutt, D. J. (2003) Psychotropic drugs, cardiac arrhythmia, and sudden death. *Journal of Clinical Psychopharmacology*, **23**, 58–77.

World Health Organization (1974) *Eighth Revision of the International Classification of Diseases and Related Health Problems (ICD–8)*. Geneva: WHO.