# Mortality Hazard Associated With Anxiolytic and Hypnotic Drug Use in the National Population Health Survey

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**Objective:** Although widely used in the general population, sleeping pills and minor tranquilizers, also known as antianxiety agents, have been associated with undesirable outcomes. Reports about the association of these drugs with an elevated mortality rate are inconsistent and controversial. This study was designed to assess the mortality hazard associated with anxiolytic and hypnotic drug use in the National Population Health Survey in Canada. It was hypothesized that anxiolytic and hypnotic drug use would be associated with an elevated mortality hazard.

**Method:** A population-based sample of 14 117 people aged 18 to 102 years participated in a longitudinal panel survey, with data collected every second year from 1994 to 2007. The primary outcome measures reported in this study are self-report use of anxiolytic and hypnotic drugs, and death.

**Results:** For respondents who reported anxiolytic or hypnotic drug use in the past month the odds of mortality were 3.22 times more (95% CI 2.70 to 3.84) than for those who did not use anxiolytic or hypnotic drugs in the past month. After controlling for confounding sociodemographic, lifestyle, and health factors (including depression), the odds ratio was reduced to 1.36 (95% CI 1.09 to 1.70) but remained significant.

**Conclusion:** Sedative drug use is associated with a small but significant increase in mortality risk. Further research is required to confirm the mechanisms by which sedative drug use increases mortality risk. Where possible, physicians should systematically consider possibilities for nonpharmacological treatment of sleep disturbances and anxiety.

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**Clinical Implications**

- Anxiolytic or hypnotic drug use is associated with an elevated mortality risk.
- Prescribing physicians and psychiatrists, as well as the public, should be better informed about the risks associated with sedative drug use.
- Physicians and psychiatrists should systematically consider and discuss with patients the possibilities for nonpharmacological treatment for sleep disturbances and anxiety.

**Limitations**

- Sedative drug use was assessed with a dichotomous, yes or no question about the use of broadly defined medications (tranquilizers and sleeping pills).
- There was no control for the presence of anxiety disorders in the prediction model of mortality.
- Data were self-reported and thus associated with numerous biases (for example, context, primacy and recency effects, suggestibility, and social desirability).

***Key Words:*** *anxiolytics, hypnotics, sleep, anxiety, mortality hazard*

Sleeping pills and minor tranquilizers, also known as antianxiety agents, are widely used in the general population. Overall population use of hypnotic medication ranges from 3% to 10%[1,2] and increases to 20% among the elderly.[3] About 4% of Canadians use benzodiazepines,[4] a class of medication commonly prescribed for anxiety and sleep problems. Although frequently prescribed for anxiety and sleep problems, benzodiazepines are associated with a wide range of adverse side effects,[5] increased risk for falls and accidents,[6–8] and exacerbated symptoms in patients who suffer from sleep-related breathing disorders.[9]

Recent research in this area has begun to investigate the association between sedative drug use and mortality hazard. Using data from the American Cancer Society's Cancer Prevention Study II, Kripke et al[10] found an elevated mortality rate associated with chronic hypnotic use, with hazard ratios of 1.35 for men and 1.22 for women, after controlling for 30 health and lifestyle risk factors. The impact of sedative drug use on hazard ratios was comparable with the impact on hazard ratios of smoking 1 to 2 packs of cigarettes per day.[11] The mortality rate remained significantly high even after controlling for insomnia and reported sleep duration.[12] Depressive symptoms, particularly suicide attempts, are potential confounds in the relation between sedative drug use and mortality. Allgulander et al[13] collected data from 221 people formerly hospitalized for dependence on sedative drugs. Thirty years after their inpatient hospital stay, 11% of men and 23% of women had died from suicide. In a follow-up study of data from 32 679 Swedish survey respondents, Allgulander and Näsman[14] found an association between chronic hypnotic use and increased suicide risk. A recent Swedish study[15] of 3523 respondents found that regular hypnotic use increased mortality risk, with hazard ratios of 4.54 for men and 2.03 for women.

A Norwegian study[16] ($n$ = 14 951) found that daily users of anxiolytic or hypnotic drugs had higher crude mortality rates than nonusers. However, the difference in mortality rate decreased markedly after adjustments were made for lifestyle and economic variables, suggesting that the finding may have been the result of residual confounding. Similarly, in a prospective Australian study of 1042 respondents aged 65 years or older, Rumble and Morgan[17] found that sleep medication users had a higher mortality rate than nonusers. However, once these authors distinguished between prescribed hypnotics and other sleep medications (for example, analgesics and over-the-counter medications), only the latter were associated with elevated mortality risk.

**Abbreviations used in this article**

| | |
|---|---|
| EE | energy expenditure |
| MET | metabolic equivalent |
| NPHS | National Population Health Survey |
| SSRI | selective serotonin reuptake inhibitor |

My study was designed to assess the mortality hazard associated with anxiolytic and hypnotic drug use in the NPHS. To gain an accurate estimate of the mortality risk associated with sedative drug use, the following confounding factors were controlled: sociodemographic characteristics (sex, age, education, income, and employment status), lifestyle (alcohol use, nicotine use, and level of physical activity), physical health, and depression. The primary hypothesis of my study was that anxiolytic and hypnotic drug use would be associated with an elevated mortality hazard.

## Method

### *Participants and Procedures*

Although my study was not approved by an institutional review board, the results are bound by Statistics Canada's confidentiality restrictions. The NPHS was designed to collect longitudinal data about health and related sociodemographic variables from members of the Canadian population. The questionnaire included questions about physical health, health services use, determinants of health, chronic health conditions, and restrictions on activity as a function of health problems. The questionnaire also gathered data about age, sex, level of education, household income, and employment status. The NPHS began in 1994 with a sample of 17 276 people aged 12 years and older from the 10 Canadian provinces. Every 2 years, respondents provided detailed and current information about their physical and mental health. My study analyzed data from the first 7 cycles of the survey (Cycle 1: 1994 to 1995; Cycle 2: 1996 to 1997; Cycle 3: 1998 to 1999; Cycle 4: 2000 to 2001; Cycle 5: 2002 to 2003; Cycle 6: 2004 to 2005; and Cycle 7: 2006 to 2007).

The sample design of the NPHS was stratified and multistaged. A minimum of 1200 households from each of the 10 Canadian provinces was included. Data were collected from 1 respondent per household. The provincial sample sizes were calculated using the Kish allocation scheme. Reliability requirements at the national and regional levels were met.[18] Further information about the sample selection procedures can be found on the Statistics Canada website.[19]

Most respondents were contacted by telephone (for example, 99% of the interviews in Cycle 7 were done by telephone). Interviewers made personal visits if requested by the respondent, or if the respondent did not have a telephone or lived in a health care institution. Interviewers also made personal visits in the course of tracing respondents. The average interview duration was just under 1 hour. The survey questions were designed for computer-assisted interviewing. The computer interview program used the respondents' answers to determine the logical follow-up questions, and indicated the type of answer required, the minimum and maximum possible

values, and instructions for the interviewer in the event of nonresponse. An on-screen error prompt allowed the interviewer to immediately correct errors and inconsistencies in data entry.

Several strategies were employed to minimize nonresponse. Interviewers were instructed to make every reasonable attempt to interview respondents. Senior interviewers, projects supervisors, or alternate interviewers followed up refusals and tried to convince respondents to continue their participation in the survey. To maximize the response rate, many refusers were recontacted during subsequent collection periods. The cumulative nonresponse rate due to failure to trace the respondent was 5.4% of the total panel.

### *Measures*

The NPHS questionnaire included questions about age, sex, level of education, employment status, income, and marital status. These variables were used as time-constant covariates and reflected the respondent's status at the time he or she entered the first cycle of the survey. If a respondent died during the observation period, his or her date of death and cause of death were recorded. The remaining variables, described below, are time-varying covariates.

*Sedative Drug Use.* This variable reflected the respondents' answers to 2 questions: In the past month, did you take tranquilizers, such as valium or ativan?; and, In the past month, did you take sleeping pills, such as imovane, nytol, or starnoc? The respondent was considered a sedative drug user for the cycle in question if he or she answered yes to either or both questions. The use of sleeping pills and the use of tranquilizers were merged into 1 category. Although hypnotic medication such as zopiclone is not likely to be used during the daytime as an anxiolytic, medications prescribed for anxiety, such as benzodiazepines, can be used at bedtime as a hypnotic.[20] Moreover, some medications, such as SSRIs with sedative properties, are used both as anxiolytics[21] and hypnotics.[20] In the absence of more detailed data on medication, it was assumed that both self-assessed categories (sleeping pills and minor tranquilizers) referred to the same pharmacological agents.

*Level of Physical Activity.* Respondents were interviewed extensively about the frequency, duration, and intensity of their involvement in 22 physical activities. The physical activity index was determined from an estimate of respondents' EE during leisure activities. EE was calculated with the values of the frequency and duration of each activity session, and the MET value of each session. MET value is an indicator of metabolic EE expressed as a multiple of resting metabolic rate. For example, an activity with a MET of 4 requires 4 times the amount of energy that is required when the body is at rest. EE values were calculated as follows:

$$\mathrm{EE\,(kcal/kg/day)} = \frac{N_1 \times D_1 \times \mathrm{MET\ value}}{365}$$

where $N_1$ is the number of times the respondent engaged in the activity$_1$ over a 12-month period, $D_1$ is the average duration in hours of the activity$_1$, and MET is the energy cost of the activity expressed as kilocalories expended per kilogram of body weight per hour of activity.

Based on EE, respondents were deemed active, moderately active, or inactive. An active status corresponded to an EE of 3 or more; about the amount of exercise required to benefit cardiovascular health. Moderately active corresponded to an EE of greater than 1.5 but less than 3; a level of activity that produces some health benefits but little cardiovascular benefit. Inactive corresponded to an EE of under 1.5.

*Drinking Habits.* This variable reflected the respondents' answer to the following question: In the past 12 months, how often did you drink alcoholic beverages? Regular drinking was defined as drinking once or more per month. Occasional drinking was defined as drinking less than once per month. Former drinkers and people who had never drunk alcohol were grouped together in the category of never drinks.

*Smoking Habits.* This variable reflected respondents' answers to 3 questions about smoking habits. Respondents were asked if they smoked daily, occasionally, or never; whether or not they had at any time smoked cigarettes; and, whether or not they had ever smoked cigarettes daily. Daily smokers were categorized as regular smokers. Occasional smokers and respondents who used to be regular smokers but had become occasional smokers were categorized as occasional smokers. Former regular or occasional smokers who no longer smoked and respondents who had never smoked were categorized as nonsmokers.

*Physical Health.* Respondents were asked whether or not they suffered from 21 chronic medical conditions. Chronic conditions were operationally defined as conditions diagnosed by a health professional that had been present or were expected to be present for at least 6 months. The following conditions were assessed: allergies (including food allergies), asthma, fibromyalgia, arthritis or rheumatism, back pain, high blood pressure, migraines, chronic bronchitis or emphysema, diabetes, epilepsy, heart disease, cancer, intestinal or stomach ulcers, side effects of a stroke, urinary incontinence, bowel disorder, Alzheimer's disease or other dementia, cataracts, glaucoma, and thyroid condition. The conditions were further classified as either respiratory system diseases (asthma and chronic bronchitis or emphysema); circulatory system diseases (high blood pressure, heart diseases, and side effects of a stroke); musculoskeletal diseases (fibromyalgia, arthritis or rheumatism, and back pain); nervous system diseases (epilepsy and migraines); endocrine, metabolic, or nutrition-related diseases (diabetes and thyroid condition); neoplasms (cancer); dementia (Alzheimer and others); and allergies, including food allergies. The remaining conditions (cataracts, glaucoma, intestinal or stomach ulcers, urinary incontinence, bowel disorder, and others)

were categorized as other. None of the conditions in the latter category had a significant impact on mortality hazard, and all were therefore excluded from the analyses.

*Depression.* This variable reflected respondents' answers to 21 questions about depressive symptoms, including feelings of sadness (including frequency and duration), loss of interest, fatigue or loss of energy, weight gain or loss, trouble sleeping, trouble concentrating, feelings of worthlessness, and thoughts about death. Respondents were asked if the symptoms were present at the time of the interview, or if they had been present during any 2-week period in the past 12 months. The total score for depression ranged from 0 to 8; higher scores reflected more symptoms.

### *Statistical Analyses*

In accordance with Statistics Canada procedures, the data in our analyses were weighted to reflect the sample design, adjustments for nonresponse, and poststratification. Kaplan-Meier survival curves were computed to compare the survival rates for people who used sedative drugs and people who did not. The curves were initially calculated with the complete sample, and subsequently recalculated by age group. The first mortality risk model was calculated using a discrete time survival analysis, with cycle (that is, 1 to 7) and sedative drug use as time-varying covariates. The second model controlled for confounding factors by including time-constant covariates (sociodemographic variables) and time-varying covariates (lifestyle and health variables). Data from all respondents were entered into the model at Cycle 1. Respondents' data continued to be entered until either their death or the end of the observation period (that is, Cycle 6, or earlier if the respondent dropped out of the study). Data from Cycle 7 (other than time of death if it occurred between Cycle 6 and Cycle 7) were not included because subsequent information about mortality was not available. Variance estimates were calculated using a bootstrap procedure, with 500 replications of the coefficients estimate. Finally, to illustrate the significance of the mortality odds ratio associated with sedative drug use, predictive values of mortality risk were computed. For these calculations, sex and age were assigned specific values and mean values were attributed to the other predictors. Statistical analyses were performed using Stata software, version 10 (StataCorp, College Station, TX).

## Results

### *Sample Description*

My study analyzed data exclusively from NPHS respondents aged 18 years and older. The sample was composed of 14 117 people aged 18 to 102 years (mean 44.09; SE 0.18), 50.90% of whom were female (Table 1). During the 12 years of observation, prevalence of hypnotic drug (sleeping pills) use ranged from 3.16% to 6.02%. Prevalence of anxiolytic drug (minor tranquilizers) use ranged from 2.99% to 4.60% over the same period. Patterns of use are presented in Table 2. Death occurred in 11.55% of the initial sample. Causes of death are reported in Table 3. Higher proportions of people using sedative drugs were observed in every category; larger differences were observed in deaths caused by neoplasms (cancers), diseases of the circulatory system, and diseases of the respiratory system.

### *Mortality Hazard as a Function of Sedative Drug Use*

Figure 1 illustrates the Kaplan-Meier survival curve as a function of sedative drug use. Nearly 90% of respondents who did not use sedative drugs survived the 12-year observation period, in comparison with about 70% of sedative drug users. The greatest differences in mortality rate between drug users and nonusers were observed in the age groups of 55 to 64 years and 65 to 74 years.

A first discrete time survival analysis regression model was computed with death as the outcome variable and time and sedative drug use as predictor variables. An odds ratio of 3.22 (95% CI 2.70 to 3.84) was obtained ($P < 0.001$). To control for potential confounding factors, sociodemographic, health, and lifestyle variables were added to the model as covariates. The results of the second model (Table 4) revealed that older age, lack of physical activity, smoking, respiratory disease, circulatory disease, endocrine system disease, cancer, and depression all significantly increased mortality risk during the observation period. Protective factors (that is, factors that decrease mortality risk) included being female, allergies, a higher income, and occasional or regular drinking. After all of these potential confounds for mortality risk were controlled, sedative drug use remained a significant predictor of death, with an odds ratio of 1.36 (95% CI 1.09 to 1.70). Sedative drug use increased mortality hazard by 36.2%. The presence of depression in the model did not have a large impact (without depression in the model, the risk ratio associated with sedative drug use was 1.40 [95% CI 1.13 to 1.75]).

### *Select Examples of Predictive Values of Death*

Predictive values of death were calculated for men and women at 3 different ages (35, 55, and 75 years), using the mean values for all other sociodemographic, health, and lifestyle covariates. The risk of death for a woman aged 35 years who did not use sedative drugs and had mean values on all remaining covariates was 0.20%, in contrast with a risk of 0.27% for a female sedative drug user of the same age. The mortality risk for a male nondrug user aged 35 years was 0.40%, in contrast with a risk of 0.54% for sedative drug users of the same age. The mortality risk for a female aged 55 years was 0.87% for nonusers and 1.19% for sedative drug users. For a man aged 55 years, the mortality risk was 1.74% for nondrug users and 2.35% for sedative drug users. Finally, the risk of death for a woman aged 75 years was 3.76% for nonusers and 5.05% for sedative drugs users. For a man of the same age, the risk of death was 7.25% for nonsedative drug users and 9.63% for sedative drug users.

**Table 1 Sociodemographic characteristics and sedative drug use**

| Characteristic | Complete sample *n* = 14 117 | Drug use = 1 (in any cycle) *n* = 830 | Drug use = 0 (in all 6 cycles) *n* = 12 758 |
|---|---|---|---|
| Female, % | 50.90 | 66.76 | 50.68 |
| Age at Cycle 1, mean (SE) | 44.09 (0.18) | 53.76 (0.79) | 43.54 (0.19) |
| | % | % | % |
| Cultural or racial background | | | |
| Caucasian | 93.23 | 96.75 | 93.66 |
| Asian | 3.56 | Supressed[a] | 3.54 |
| Black | 1.13 | Supressed[a] | 1.16 |
| Native American | 1.17 | Supressed[a] | 1.20 |
| Multiracial | 0.48 | Supressed[a] | 0.47 |
| Born in Canada | 84.71 | 86.87 | 84.98 |
| Education | | | |
| Did not complete high school | 25.97 | 38.85 | 25.07 |
| Completed high school | 16.29 | 13.56 | 16.42 |
| Some post-secondary education | 25.57 | 20.46 | 26.03 |
| Post-secondary degree | 32.17 | 27.14 | 32.49 |
| Employment status | | | |
| Employed | 61.80 | 31.31 | 63.47 |
| Unemployed | 4.94 | 2.94 | 5.00 |
| Retired or other | 33.26 | 65.75 | 31.52 |
| Family income, $ | | | |
| <20 000 | 21.04 | 36.94 | 20.20 |
| 20 000–39 999 | 28.58 | 28.18 | 28.58 |
| 40 000–59 999 | 25.16 | 16.69 | 25.72 |
| 60 000–79 999 | 12.65 | 8.77 | 12.83 |
| >80 000 | 12.57 | 9.43 | 12.66 |
| Marital status | | | |
| Married or common law | 65.92 | 57.38 | 66.23 |
| Single | 20.52 | 15.21 | 20.84 |
| Widowed | 5.98 | 14.16 | 5.58 |
| Separated or divorced | 7.57 | 13.25 | 7.35 |
| Hypnotic drug use | | | |
| Cycle 1 | 3.16 | 57.62 | — |
| Cycle 2 | 3.84 | 63.01 | — |
| Cycle 3 | 4.08 | 65.75 | — |
| Cycle 4 | 5.24 | 67.03 | — |
| Cycle 5 | 5.34 | 60.14 | — |
| Cycle 6 | 4.18 | 45.48 | |
| Anxiolytic drug use | | | |
| Cycle 1 | 3.08 | 56.18 | — |
| Cycle 2 | 2.99 | 48.97 | — |
| Cycle 3 | 3.01 | 48.58 | — |
| Cycle 4 | 3.66 | 46.80 | — |
| Cycle 5 | 4.60 | 51.96 | — |
| Cycle 6 | 4.18 | 45.48 | — |

[a] To maintain confidentiality (too few observations)

**Table 2 Proportions of respondents showing different patterns of sedative drug use during the 12-year observation period**

| Number of times respondents answered yes to use of sleeping pills in the past month | % |
|---|---|
| 0 | 85.68 |
| 1 | 8.45 |
| 2 | 2.76 |
| 3 | 1.56 |
| 4 | 0.83 |
| 5 | 0.38 |
| 6 | 0.33 |
| **Number of times respondents answered yes to use of minor tranquilizers in the past month** | **%** |
| 0 | 88.93 |
| 1 | 6.88 |
| 2 | 2.07 |
| 3 | 0.95 |
| 4 | 0.45 |
| 5 | 0.35 |
| 6 | 0.37 |
| **Patterns of use** | **%** |
| No sedative drugs | 79.88 |
| Only hypnotics | 9.05 |
| Only anxiolytics | 5.80 |
| Both anxiolytics and hypnotics | 5.27 |

## Discussion

My study was designed to assess the mortality hazard associated with anxiolytic and hypnotic drug use, while controlling for potentially confounding health and lifestyle variables. Results confirmed the hypothesis: respondents who reported use of anxiolytic or hypnotic drugs in the past month had a small elevation of their mortality ratio, even after controlling for confounding sociodemographic, lifestyle, and health factors (including depression).

These results are similar to results published by Kripke et al[10] based on data collected in the 1980s. While it is not unreasonable to expect a decrease in mortality rate as a function of the more sophisticated drugs presently on the market, such a decrease was not apparent in the NPHS. My study made a unique contribution to the literature in this area by demonstrating that the elevated mortality risk persisted after a potential confounding factor (depression) was controlled. In the present findings, depressive symptoms had a small contribution to the prediction of mortality, and their inclusion in the prediction model had a negligible impact on the mortality hazard associated with sedative drug use.

Several possible explanations have been proposed in the literature for the small but significant relation between sedative drug use and premature death. One explanation implicates the side effects of benzodiazepines, the primary class of medication marketed for treating anxiety and sleep problems. This class of medication is associated with impairments in reaction time, psychomotor coordination, performance, memory, and other cognitive functions,[5] increased risk for

**Table 3 Causes of death using the International Classification of Diseases, 10th Revision**

| Death and causes of death | Complete sample *n* = 14 117 % | Drug use = 1 (in any cycle) *n* = 830 % | Drug use = 0 (in all 6 cycles) *n* = 12 758 % |
|---|---|---|---|
| Deaths | 11.55 | 15.66 | 10.52 |
| Causes of death[a] | | | |
| Certain infectious and parasitic diseases (A00–B99) | 0.13 | 0.21 | 0.12 |
| Neoplasms (C00–D48) | 3.33 | 4.27 | 3.10 |
| Endocrine, nutritional and metabolic diseases (E00–E90) | 0.36 | 0.38 | 0.36 |
| Diseases of the nervous system (G00–G99) | 0.39 | 0.52 | 0.35 |
| Diseases of the circulatory system (I00–I99) | 3.27 | 4.20 | 3.03 |
| Diseases of the respiratory system (J00–J99) | 0.88 | 1.75 | 0.67 |
| Diseases of the digestive system (K00–K93) | 0.29 | 0.34 | 0.28 |
| External causes of morbidity and mortality (V01–Y98) | 0.65 | 0.92 | 0.58 |
| Other conditions[b] (D50–D89; F00–F99; L00–N99; Q00–U99) | 0.65 | 0.92 | 0.58 |

[a] The code represents the disease or injury that initiated the sequence of events leading directly to death, or the circumstances of the accident or the violence that produced the fatal injury.

[b] The remaining categories were merged together for confidentiality reasons (too few observations).

**Figure 1 Survival as a function of anxiolytic or hypnotic drug use (complete sample [*n* = 14 117] and by age group)**

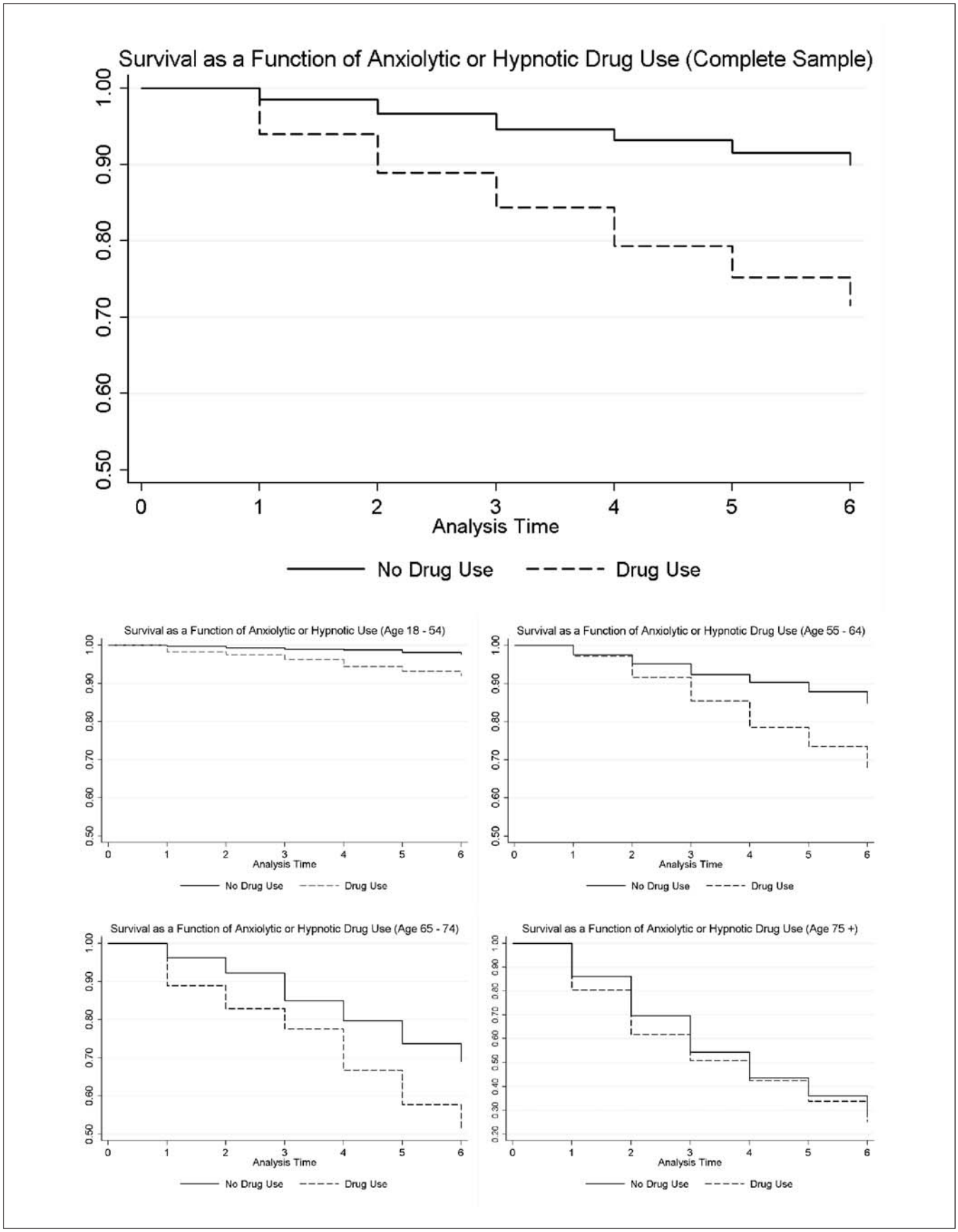

**Table 4 Mortality hazard as a function of sedative drug use**

| Variable | OR | SE | z | *P* | 95% CI |
|---|---|---|---|---|---|
| Sedative drug use | 1.362 | 0.153 | 2.76 | 0.006 | 1.093–1.698 |
| Age | 1.077 | 0.021 | 3.80 | <0.001 | 1.037–1.119 |
| Age (squared) | 1.000 | 0.000 | 0.54 | 0.59 | 1.000–1.000 |
| Female | 0.499 | 0.042 | –8.20 | <0.001 | 0.423–0.590 |
| Education | | | | | |
| Completed high school[a] | 1.064 | 0.151 | 0.44 | 0.66 | 0.805–1.407 |
| Some post-secondary education[a] | 0.933 | 0.112 | –0.57 | 0.57 | 0.737–1.182 |
| Post-secondary degree[a] | 1.033 | 0.122 | 0.28 | 0.78 | 0.820–1.302 |
| Employment status | | | | | |
| Unemployed[b] | 0.960 | 0.210 | –0.19 | 0.85 | 0.625–1.475 |
| Retired or other[b] | 1.001 | 0.145 | 0.01 | 0.99 | 0.754–1.330 |
| Income, $ | | | | | |
| 20 000–39 999[c] | 0.833 | 0.085 | –1.79 | 0.07 | 0.681–1.018 |
| 40 000–59 999[c] | 0.665 | 0.099 | –2.73 | 0.006 | 0.496–0.892 |
| 60 000–79 999[c] | 0.919 | 0.176 | –0.44 | 0.66 | 0.631–1.338 |
| >80 000[c] | 0.415 | 0.100 | –3.66 | <0.001 | 0.258–0.665 |
| Marital status | | | | | |
| Single[d] | 1.298 | 0.187 | 1.81 | 0.07 | 0.978–1.722 |
| Widowed[d] | 1.235 | 0.133 | 1.96 | 0.05 | 0.999–1.526 |
| Separated or divorced[d] | 1.221 | 0.197 | 1.24 | 0.22 | 0.890–1.677 |
| Moderately active[e] | 1.009 | 0.179 | 0.05 | 0.96 | 0.712–1.429 |
| Inactive[e] | 1.499 | 0.239 | 2.54 | 0.01 | 1.096–2.050 |
| Occasional drinker[f] | 0.741 | 0.085 | –2.60 | 0.01 | 0.591–0.930 |
| Regular drinker[f] | 0.676 | 0.065 | –4.06 | <0.001 | 0.560–0.817 |
| Occasional smoker[g] | 1.351 | 0.302 | 1.34 | 0.18 | 0.871–2.096 |
| Regular smoker[g] | 1.995 | 0.210 | 6.58 | <0.001 | 1.623–2.452 |
| Medical conditions | | | | | |
| Respiratory | 1.552 | 0.172 | 3.97 | <0.001 | 1.249–1.929 |
| Circulatory | 1.316 | 0.115 | 3.13 | 0.002 | 1.108–1.563 |
| Musculoskeletal | 1.086 | 0.099 | 0.91 | 0.36 | 0.909–1.299 |
| Nervous | 0.846 | 0.161 | –0.88 | 0.38 | 0.582–1.229 |
| Endocrine, metabolic, or nutritional | 1.276 | 0.157 | 1.99 | 0.047 | 1.003–1.624 |
| Neoplasms (cancer) | 4.294 | 0.614 | 10.19 | <0.001 | 3.242–5.686 |
| Dementia | 2.209 | 0.931 | 1.88 | 0.06 | 0.965–5.057 |
| Allergies (including food allergies) | 0.772 | 0.082 | –2.44 | 0.02 | 0.627–0.951 |
| Depression scale | 1.072 | 0.032 | 2.32 | 0.02 | 1.011–1.137 |
| Time | 1.124 | 0.030 | 4.36 | <0.001 | 1.066–1.185 |

[a] Reference category is did not complete high school
[b] Reference category is employed
[c] Reference category is income <$20 000
[d] Reference category is married or common law
[e] Reference category is active
[f] Reference category is never drinks
[g] Reference category is nonsmoker

falls and accidents,[6–8] and a depressant effect on the respiratory system that may aggravate sleep-related breathing disorders, particularly in patients with chronic obstructive pulmonary disease or history of cardiac failure.[9] Further, people with anxiety and sleep problems may self-medicate with alcohol or other drugs[22,23]; these substances can intensify the depressant effects of benzodiazepines. Finally, sedative drugs are central nervous system depressants, and may impair self-protective judgment, increasing suicide risk.[13]

New hypnotics, such as zopiclone or zaleplon, have more specific hypnotic effects and fewer unwanted side effects; however, they do not eliminate all of the undesirable outcomes associated with benzodiazepine use.[24] Further, although preliminary, recent findings suggested increased risks of depression, skin cancer, and infections associated with use of new hypnotics (that is, zopiclone, zolpidem, zaleplon, eszopiclone, and ramelteon).[25–27]

SSRIs are a further class of medication widely used to treat anxiety and sleep problems. In addition to sexual dysfunction, weight gain and loss, and emotional detachment,[28] suicidal ideation and suicide attempts are included in the list of side effects associated with this class of medications.[29] Finally, natural products and over-the-counter medications are frequently used to self-treat anxiety and insomnia.[22] Although little is known about the safety of short- or long-term use of these medications, Rumble and Morgan[17] observed a higher mortality risk in users of analgesics and over-the-counter medication than in users of prescription sleep medication. In my findings, the main causes of death associated with sedative drug use were neoplasms (cancer), diseases of the circulatory system, and diseases of the respiratory system. Although these findings do not allow causality inference, they offer interesting research avenues to understand the mechanisms through which sedative drug use can lead to premature death.

Several limitations must be considered in the interpretation of my study's findings. First, sedative drug use was assessed with a dichotomous, yes or no question about the use of broadly defined medications (tranquilizers and sleeping pills). This nonspecificity allowed for the inclusion of a wide diversity of habits among drug users; habits among respondents in the drug use group could conceivably have ranged from a one-time use of over-the-counter antihistamine to daily benzodiazepine use for the past 20 years. However, it is noteworthy that the findings remained significant despite the probable inclusion of nonharmful drug use in the drug users group. A second limitation to this study is the absence of a control for anxiety disorders in the risk model. Anxiety disorders are often treated with anxiolytics and have been, to some extent, associated with an elevated suicidal risk. Finally, interpretations are limited by the use of self-report data about medical conditions. Self-report data are associated with numerous biases (for example, context, primacy and recency effects, suggestibility, and social desirability).

The relation found in this study between elevated mortality hazard and sedative drug use, although of small magnitude, could have important clinical implications. First, prescribing physicians and psychiatrists should carefully consider mortality risk before prescribing or renewing prescriptions for anxiolytic and hypnotic drugs for outpatients. Second, the public should be better informed about the risks associated with sedative drug use. Finally, physicians and psychiatrists should systematically consider and discuss with patients the possibilities for nonpharmacological treatment for sleep disturbances and anxiety. Cognitive-behavioural therapy, in particular, has been proven to be as effective or more effective than pharmacotherapy for many sleep and anxiety disorders, including chronic insomnia,[30] generalized anxiety disorder,[31] posttraumatic stress disorder,[32] panic disorder,[33] social phobia,[34] and specific phobias.[35] Combined short-term pharmacological and psychological treatment also constitutes a promising strategy for decreasing anxiety and promoting sleep. In conclusion, given the elevated mortality risk associated with sedative drug use, when possible, nonpharmacological options for managing sleep disturbances and anxiety should be considered.

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## Résumé : Le risque de mortalité associé à l'utilisation d'anxiolytiques et d'hypnotiques selon l'Enquête nationale sur la santé de la population

**Objectif :** Bien que largement utilisés dans la population générale, les somnifères et les tranquillisants mineurs, aussi connus comme agents anxiolytiques, ont été associés avec des résultats indésirables. Les rapports faisant état de l'association de ces médicaments avec des taux de mortalité élevés sont incohérents et controversés. Cette étude était conçue pour évaluer le risque de mortalité associé à l'utilisation d'anxiolytiques et d'hypnotiques selon l'Enquête nationale sur la santé de la population du Canada. L'hypothèse émise était que l'utilisation d'anxiolytiques et d'hypnotiques serait associée à un risque de mortalité élevé.

**Méthode :** Un échantillon dans la population de 14 117 personnes âgées de 18 à 102 ans a participé à une enquête longitudinale par panel, les données étant recueillies aux deux ans de 1994 à 2007. Les principales mesures des résultats rapportées dans cette étude sont l'utilisation autodéclarée d'anxiolytiques et d'hypnotiques, et les décès.

**Résultats :** Pour les répondants qui ont déclaré avoir utilisé des anxiolytiques ou des hypnotiques le mois précédent, les probabilités de mortalité étaient 3,22 fois plus élevées (IC à 95 % 2,70 à 3,84) que pour ceux qui n'avaient pas utilisé d'anxiolytiques ou d'hypnotiques le mois précédent. Après contrôle pour des facteurs confusionnels sociodémographiques, de style de vie, et de santé (incluant la dépression), le rapport de cotes était réduit à 1,36 (IC à 95 % 1,09 à 1,70) mais demeurait significatif.

**Conclusion :** L'utilisation de sédatifs est associée à une augmentation modeste mais significative du risque de mortalité. Il faut plus de recherche pour confirmer les mécanismes par lesquels l'utilisation de sédatifs accroît le risque de mortalité. Autant que possible, les médecins devraient systématiquement considérer les possibilités de traitement non pharmacologique des troubles du sommeil et de l'anxiété.