Short- and long-term mortality following hypnotic use

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Abstract
Potential long-term consequences of hypnotics remain controversial. We used the prospective Swedish National March Cohort, a study based on 41,695 participants with a mean follow-up duration of 18.9 years. Logistic regression models and Cox proportional hazards models with attained age as timescale were used to assess associations of hypnotic use with short- and long-term mortality. The proportion of subjects who initiated or discontinued hypnotic use during follow-up was substantial. All groups of hypnotics were associated with increased mortality within 2 years after a first prescription, with an overall OR of 2.38 (95% CI, 2.13–2.66). The association was more pronounced among subjects younger than 60 years (OR, 6.16; 95% CI, 3.98–9.52). There was no association between hypnotic use and long-term mortality. The association between hypnotic use and increased mortality was thus restricted to a relatively short period after treatment initiation, and may be explained in terms of confounding by indication.

KEYWORDS
hypnotic use, insomnia, mortality, prospective cohort study

1 | INTRODUCTION

Insufficient sleep duration and sleep disorders such as insomnia are highly prevalent and often co-occur with chronic medical conditions and psychiatric disorders. One-third of the Swedish population reported insufficient sleep in 2015, and prescriptions of hypnotics have increased by 40% between 2001 and 2015 (SCB, 2019). The market for insomnia medications is dominated by benzodiazepines and Z-drugs (zopiclone, zolpidem and zaleplon). These drugs act as positive allosteric modulators at the gamma-aminobutyric acid (GABA)A binding site, potentiating GABA’s inhibitory effect. Both categories of drugs have been associated with numerous adverse effects, such as impairment in psychomotor performance, respiratory suppression, tolerance and dependence, withdrawal symptoms and potential for abuse.

In the large prospective Cancer Prevention Study I and II of the American Cancer Society, use of hypnotics was associated with increased mortality (Kripke et al., 1998; Kripke, Simons, Garfinkel, & Hammond, 1979), a finding replicated in several studies (Obiora, Hubbard, Sanders, & Myles, 2012; Sivertsen, Madsen, Salo, Tell, & Overland, 2015; Weich et al., 2014). Intentional or accidental overdoses of hypnotics can be lethal and hypnotics are likely to contribute to some accidents (Gustavsen, Bramness, & Skurtveit, 2008; Leipzig, Cumming, & Tinetti, 1999). However, previous studies have
not distinguished between short- and long-term mortality. Beside the
association with all-cause mortality, hypnotic use has been associated
with specific causes of death, such as cardiovascular disease (Mallon,
Broman, & Hetta, 2009) and cancer (Kripke, 2009; Kripke, Langer, &
Kline, 2012). Using a large Swedish cohort with a mean follow-up time
of 18.9 years, we aimed to study the association of hypnotics with
short- and long-term all-cause and cause-specific mortality.

2 | METHODS

We used the Swedish National March Cohort (Trolle Lagerros,
Hantikainen, & Mariosa, 2017), designed to investigate associations
between lifestyle factors and chronic diseases. The study was es-

established in September 1997 during a 4-day nationwide fundraising
event for the Swedish Cancer Society. Nearly 3,600 Swedish cities
and villages took part in the event. All participants were invited to
fill out a 36-page questionnaire regarding demographic, lifestyle and
medical information. They also provided their national registration
number, an individually unique identifier assigned to all Swedish resi-
dents, which enables follow-up by linkage to multiple nationwide,
continuously updated and essentially complete databases.

In total, 43,863 participants completed the questionnaire. Those
with incorrect national registration numbers were excluded (n = 11),
as were those who were younger than 18 years (n = 1,732) or had
emigrated or died (n = 55) before the start of follow-up. We also
excluded subjects who did not provide information regarding hyp-
notic use (n = 370). Our final study population thus included 41,695
subjects followed prospectively for all-cause and disease-specific
mortality until the end of April 2018. The study was approved by
the Regional Ethics Committee in Stockholm and all participants pro-
vided written informed consent.

The cohort was followed from baseline on October 1, 1997 until
date of death, emigration or April 30, 2018, whichever occurred
first. Using the national registration numbers, mortality data were
obtained by linkage to the Swedish Cause of Death Register held by
the National Board for Health and Welfare. A total of 9,093 deaths
occurred during the follow-up period. Information regarding diag-
noses of cardiovascular disease (I00-I99), cancer (C00-C97) and
psychiatric disorders (F00-F99) was obtained from the Swedish
National Patient Registers and the Swedish Cancer Register.

Hypnotic use at baseline was assessed by asking the partici-
pants to estimate how often they took sleeping pills. The response
alternatives were never, seldom, sometimes, mostly or always. The
reference group was those who never used hypnotics. Information
regarding hypnotic use during follow-up was obtained from the
Swedish Drug Registry, in which all prescriptions dispensed in
Swedish pharmacies in 2005 or later are registered. Hypnotics were
categorized into benzodiazepines (N05CD), Z-hypnotics (N05CF)
and other hypnotics (N05CM).

2.1 | Statistical analyses

Differences in baseline variables across categories of hypnotic
use frequency were assessed using one-way analysis of variance
(ANOVA) for continuous variables and the Kruskal-Wallis test for
categorical variables.

2.1.1 | Short-term hypnotic use

We used logistic regression models to study the association between
hypnotic use at baseline and all-cause and cause-specific mortality
during the first 4 years of follow-up. Among subjects who were alive
in January 2005, we used logistic regression to assess mortality risk
during 2005–2006 among those who collected prescriptions of hyp-
notics in 2005, compared with those who never collected a prescrip-
tion of hypnotics. We next assessed mortality during 2007–2008
among those who collected their first prescription of hypnotics in
2007 compared to those who never collected a prescription of hyp-
notics. In the same way, we assessed mortality within 2 years after

Assessment of short-term mortality

FIGURE 1  Assessment of short-term mortality
collecting a first prescription of a hypnotic during 2009, 2011, 2013 and 2015. We then pooled the results from these six logistic regression models (Figure 1). The analyses were stratified by age (<60 years or 60+ years) and gender.

### 2.1.2 Long-term hypnotic use

We used Cox proportional hazards models with attained age as time-scale to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for hypnotic users at baseline, compared to those who never used hypnotics. We assessed the proportionality hazard assumption, based on the Schoenfeld residual plots and statistical tests.

Using logistic regression, subjects who collected prescriptions of hypnotics during 2005 were compared with those who never collected a prescription of hypnotics during follow-up, with regard to mortality risk in a 2-year interval from the onset of 2005. Participants who collected their first prescription of hypnotics during 2006–2007 were compared with those who never collected a prescription of hypnotics, with regard to mortality risk in a 2-year interval from the onset of 2007. Similarly, new users who collected their first prescription of hypnotics in 2008–2009, 2010–2011 and 2012–2013 were compared with those who never collected a prescription of hypnotics. All users of hypnotics between 2005 and 2013 were thus included in the analyses (Figure 2).

We also assessed mortality risk using a logistic regression model in which subjects were categorized based on their hypnotic consumption in 2005–2008, 2009–2011 and 2012–2013 were compared with those who never collected a prescription of hypnotics. All users of hypnotics between 2005 and 2013 were thus included in the analyses (Figure 2).

### 2.1.3 Potential confounding variables

The Cox regression models with self-reported hypnotic use as the exposure were adjusted for potential confounding variables, including sex, occupation, education, body mass index (BMI), physical activity, smoking and alcohol consumption. The Cox regression models were also adjusted for a diagnosis of cardiovascular disease and cancer, and for psychiatric conditions.

The logistic regression models, in which subjects who had died before 2005 were excluded, were adjusted for sex, education, BMI at baseline, ever smoking at baseline, cardiovascular disease, cancer, psychiatric conditions, and medication with antipsychotics, sedatives and antidepressants.

The proportion of missing data in the potential confounding variables was 4.6% for BMI, 1.4% for ever smoking, and less than 1% for occupational level, educational level, physical activity and alcohol consumption. We therefore conducted supplementary analyses after imputing missing data using the multiple imputation chained equation procedure. We also conducted sensitivity analyses in which we further adjusted for habitual sleep duration and insomnia. Insomnia was defined as mostly or always experiencing any of the nocturnal insomnia symptoms (difficulties initiating sleep, difficulties maintaining sleep and early-morning awakenings) in combination with mostly or always experiencing symptoms of non-restorative sleep (not rested at awakening and daytime sleepiness). All analyses were performed using Statistical Analysis System 9.4.

### 3 RESULTS

Characteristics of participants at baseline, overall and by frequency of hypnotic use, are presented in Table 1. Hypnotic use was highly correlated with sleep duration and insomnia. Generally, hypnotic users were older, less educated and less physically active. They were more often diagnosed with cardiovascular disease, cancer or psychiatric conditions, compared to subjects who never used hypnotics.

In Table 2, we illustrate how hypnotic use changed between time periods. The proportion of subjects who initiated or discontinued hypnotic use during follow-up was substantial.

### 3.1 Short-term hypnotic use

Self-reported hypnotic use was associated with a significantly increased mortality confined to the first 2 years of follow-up (p for
Compared to subjects who never collected prescriptions of hypnotics, short-term mortality was increased after collecting a first prescription of hypnotics. Within 2 years after collection of a first prescription of hypnotics, all-cause mortality was increased 2.38-fold; benzodiazepines increased risk 5-fold, whereas Z-drugs and other hypnotics doubled the risk (Table 4). Mortality due to cancer was increased 4-fold, whereas mortality due to cardiovascular disease and other causes was increased by 30% and 60%, respectively. Mortality due to external causes, respiratory diseases, neurologic diseases and psychiatric diseases (mainly Alzheimer’s disease and other kinds of dementia) was more common among hypnotic users. The mortality rate for each of these causes of death during each 2-year period was less than 0.1% among non-users, whereas the mortality rate was more than doubled among hypnotic users (data not shown).

The overall association between hypnotic use and short-term mortality was increased about 6-fold among participants younger than 60 years (odds ratio [OR], 6.16; 95% CI, 3.98–9.52) and 2-fold among those aged 60 years or older (OR, 2.22; 95% CI, 1.98–2.49). The association was also stronger among men (OR, 3.05; 95% CI, 2.61–3.57) than among women (OR, 2.20; 95% CI, 1.89–2.57) (data not shown).

### 3.2 Long-term hypnotic use

Overall, self-reported hypnotic use was associated with long-term increased mortality during a mean follow-up time of 18.9 years (SD 4.1). Mortality increased with increasing frequency of hypnotic use (Table 5). However, when we studied mortality risk in 2-year time intervals after collecting a first prescription of hypnotics, the increased mortality risk was confined to a relatively short period following the initiation of hypnotic use, with no association between hypnotic use and long-term mortality (Table 6).

Similarly, when subjects were categorized based on history of collected prescriptions of hypnotics between 2005 and 2012, mortality was increased only in subjects who had recently started using hypnotics (Table 7).

Our results remained stable in analyses including multiple imputed data (data not shown). Our results also remained similar after adjustment for habitual sleep duration and insomnia (data not shown).

### 4 DISCUSSION

In our prospective cohort study, comprising 41,695 participants, initiation of hypnotic use was associated with increased short-term
Table 2: Collected prescriptions of hypnotics during different time periods among participants in the Swedish March Cohort Study

| Time Period                 | N  | Hypnotics at baseline | Non-pharmacologic interventions |
|-----------------------------|----|-----------------------|---------------------------------|
| January 2009 to December 2012 | 38,474 | 6,913 (17) | Non-pharmacologic interventions |
| January 2005 to December 2008 | 39,986 | 5,719 (14) | Non-pharmacologic interventions |
| January 2013 to December 2016 | 36,343 | 4,044 (11) | Non-pharmacologic interventions |

Note: The cohort comprised 41,695 participants at baseline in October 1997. Self-reported use of hypnotics at baseline; N = 5,596 (13%). New users were those who had not previously collected prescriptions of hypnotics. Some users collected prescriptions of combinations of hypnotics.

The impact of hypnotic use on long-term mortality is another potential explanation. An association of hypnotics with excess mortality may arise due to confounding by indication because chronic illness increases the need for hypnotic use. Impaired sleep has indeed been suggested to represent an early sign of cancer and often precedes a cancer diagnosis (Garland, Irwin, Posner, & Perlis, 2018). Symptomatic treatment, including insomnia treatment, is also one of the primary goals in palliative care. This is in agreement with our finding of a strong association between hypnotic use and short-term mortality due to cancer and cardiovascular disease. All categories of hypnotics, with differing mechanisms of action, were associated with increased short-term mortality. This lack of specificity supports the view that the association between hypnotics and mortality is non-causal and mainly due to confounding by indication. However, adverse effects of hypnotics, such as respiratory suppression and impairment in psychomotor performance, may contribute to increased short-term mortality. Whether an association between hypnotics and cancer is causal or due to confounding or reverse causation has been debated (Neutel & Johansen, 2015), and is of great importance considering the extensive use of these drugs. We found no association between hypnotic use and long-term mortality, which contradicts the biologic impact of hypnotics on cancer induction or progression of pre-existing cancers.

Non-pharmacologic interventions are the first-line therapy for adults with insomnia. Numerous clinical trials provide evidence that cognitive behavioural therapy, traditionally delivered in either individual or group settings, is an effective treatment for insomnia (Trauer, Qian, Doyle, Rajaratnam, & Cunnington, 2015). Internet-based cognitive behavioural therapy seems to be equally effective and could make the treatment more available in order to better meet population needs (Seyffert et al., 2016). Nevertheless, hypnotics for short-term use may be indicated for acute onset insomnia due to an identifiable precipitant, such as a cancer diagnosis. Long-term treatment has been suggested for those with severe insomnia that...
is unresponsive to other approaches (Winkelman, 2015). In order to prevent and relieve unnecessary suffering, hypnotic medication may also be part of palliative care.

Insomnia is associated with a chronic physiologic arousal (Bonnet & Arand, 2010) and may increase the risk of medical disorders such as hypertension (Fernandez-Mendoza, Vgontzas, & Liao, 2012), cardiac disease (Laugsand, Vatten, Platou, & Janszky, 2011) and diabetes (Vgontzas et al., 2009). Although insomnia often co-occurs with psychiatric disorders such as depression and anxiety (Baglioni et al., 2011), a recent meta-analysis

### TABLE 3

Logistic regression analyses with estimated odds ratio (OR) and 95% confidence interval (CI) for all-cause and cause-specific mortality among subjects who reported hypnotic use at baseline, compared to those who never used hypnotics at baseline

| Hypnotics | Mortality between October 1997 and December 1999 |  |  |  |  | p value for trend |
|-----------|----------------------------------------------|---|---|---|---|------------------|
|           | N                                           | Cause of death | Deaths (%) | OR (95% CI)a | OR (95% CI)b |          |
| No        | 36,099                                      | All-cause       | 277 (0.8)  | 1.0 (reference) | 1.0 (reference) | .02    |
| Yes       | 5,596                                       |                | 107 (1.9)  | 1.56 (0.24–1.98) | 1.40 (1.11–1.78) |        |
| No        | 36,099                                      | Cardiovascular disease | 90 (0.3)  | 1.0 (reference) | 1.0 (reference) | .18    |
| Yes       | 5,596                                       |                | 28 (0.5)   | 1.19 (0.77–1.85) | 1.05 (0.67–1.64) |        |
| No        | 36,099                                      | Cancer         | 149 (0.4)  | 1.0 (reference) | 1.0 (reference) | .005   |
| Yes       | 5,596                                       |                | 63 (1.1)   | 1.67 (1.23–2.28) | 1.57 (1.15–2.14) |        |
| No        | 36,099                                      | Other          | 38 (0.1)   | 1.0 (reference) | 1.0 (reference) | .08    |
| Yes       | 5,596                                       |                | 16 (0.3)   | 2.04 (1.11–3.75) | 1.56 (0.83–2.92) |        |

aAdjusted for age and gender.
bAdjusted for age, gender, educational level, occupational status, smoking, alcohol consumption, body mass index, physical activity, cardiovascular disease, cancer and psychiatric disorders.
cThe p value for trend was calculated with hypnotics as an interval variable (0 = never, 1 = seldom, 2 = sometimes, 3 = mostly/always).

### TABLE 4

Pooled results from logistic regression analyses with estimated odds ratio (OR) and 95% confidence interval (CI) for all-cause and cause-specific mortality within 2 years after collecting a first prescription of hypnotics between January 2005 and December 2015, compared with subjects who never collected prescriptions of hypnotics

| Hypnotic use | Type of hypnotic | N       | Cause of death | Deaths | OR (95% CI)a | OR (95% CI)b |
|--------------|------------------|---------|----------------|--------|--------------|--------------|
| No None      | None             | 157,622 | All-cause      | 3,143  | 1.0 (reference) | 1.0 (reference) |
| Yes Any      | N05CD (benzodiazepines) | 6,624  |                | 561    | 2.57 (2.36–2.79) | 2.38 (2.13–2.66) |
|              | N05CD (Z-drugs)  | 554     |                | 88     | 7.64 (5.81–10.0)  | 5.09 (3.80–6.82)  |
|              | N05CM (other hypnotics) | 5,709  |                | 487    | 2.32 (2.11–2.56)  | 2.05 (1.86–2.27)  |
|              | 2017             |         |                | 203    | 3.43 (2.87–4.09)  | 2.52 (2.10–3.02)  |
| No None      | Cardiovascular disease | 157,622 |                | 1,182  | 1.0 (reference) | 1.0 (reference) |
| Yes Any      | N05CD (benzodiazepines) | 6,624  |                | 150    | 1.61 (1.32–1.97)  | 1.31 (1.08–1.59)  |
|              | N05CD (Z-drugs)  | 554     |                | 1,063  | 1.0 (reference) | 1.0 (reference) |
|              | N05CM (other hypnotics) | 6,624  |                | 275    | 4.35 (3.78–5.01)  | 3.96 (3.41–4.60)  |
| No None      | Other            | 157,622 |                | 136    | 2.49 (2.02–3.07)  | 1.61 (1.32–1.98)  |
| Yes Any      | N05CD (benzodiazepines) | 6,624  |                | 898    | 1.0 (reference) | 1.0 (reference) |

aAdjusted for age and gender.
bAdjusted for age, gender, educational level, body mass index, smoking, cardiovascular disease, cancer, psychiatric disorders, sedatives, neuroleptic medication and antidepressants. Results from the logistic regression models are presented in Tables S1–S6.
concluded that insomnia increases the risk of incident depression (Fang, Tu, Sheng, & Shao, 2019) and suicide (Bjorngaard, Bjerkeset, Romundstad, & Gunnell, 2011; Lin, Lai, & Perng, 2018). Whether hypnotic medication reduces this excess risk deserves further study.

The strengths of this prospective cohort study are the large sample size, and the long and almost complete follow-up ascertained by linking baseline information with nationwide, continuously updated registers. A limitation is that self-reported information regarding lifestyle factors was only measured at baseline, and potential changes in lifestyle habits during the follow-up period would go undetected. The baseline measurement of self-reported hypnotic use was crude and did not allow distinction between prescribed and non-prescribed hypnics. However, information was available for all prescriptions dispensed in Swedish pharmacies in 2005 or later, and we had the possibility to study the association between hypnotics and mortality in detail.

In conclusion, the association between hypnotic use and increased mortality was restricted to a relatively short period after treatment initiation and may to be explained by confounding by indication.

**CONFLICT OF INTEREST**
The authors report no conflict of interest.
| Time periods of hypnotic use | All-cause mortality 2013–2014 | Cause-specific mortality 2013–2014 |
|-----------------------------|-------------------------------|----------------------------------|
|                             | N                              | Deaths (%) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
|                             | 2005–2008                      | 2009–2012   | Cardiovascular disease | Cancer | Other |
| No                          | 26,091                         | 568 (2.2)  | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Yes                         | 1,482                          | 68 (4.6)   | 1.64 (1.25–2.15) | 1.25 (0.94–1.66) | 1.36 (0.87–2.10) | 1.00 (0.59–1.68) | 1.25 (0.80–1.96) |
| No                          | 2,464                          | 183 (7.4)  | 2.13 (1.77–2.56) | 1.68 (1.38–2.03) | 1.58 (1.17–2.14) | 1.49 (1.06–2.09) | 1.66 (1.22–2.26) |
| Yes                         | 4,013                          | 295 (7.4)  | 1.61 (1.38–1.89) | 1.23 (1.04–1.45) | 1.16 (0.90–1.50) | 1.34 (1.01–1.78) | 1.14 (0.87–1.50) |

| Time periods of hypnotic use | All-cause mortality 2015–2016 | Cause-specific mortality 2015–2016 |
|-----------------------------|-------------------------------|----------------------------------|
|                             | N                              | Deaths (%) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
|                             | 2005–2008                      | 2009–2012   | Cardiovascular disease | Cancer | Other |
| No                          | 25,523                         | 669 (2.6)  | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Yes                         | 1,414                          | 72 (5.1)   | 1.60 (1.23–2.10) | 1.08 (0.81–1.43) | 1.14 (0.74–1.77) | 1.28 (0.79–2.09) | 0.85 (0.54–1.33) |
| No                          | 2,281                          | 164 (7.2)  | 1.71 (1.42–2.08) | 1.24 (1.02–1.52) | 1.18 (0.94–1.89) | 1.12 (0.76–1.65) | 1.09 (0.80–1.49) |
| Yes                         | 3,718                          | 302 (8.1)  | 1.49 (1.28–1.74) | 1.03 (0.87–1.21) | 1.17 (0.92–1.49) | 0.88 (0.63–1.22) | 0.96 (0.75–1.23) |

\(^a\)Adjusted for gender.
\(^b\)Adjusted for gender, educational level, ever smoking at baseline, body mass index at baseline, cardiovascular disease, cancer, psychiatric disorders, neuroleptic medication, sedatives and antidepressants. Subjects who initiated hypnotic use after 2012 were excluded from these analyses.
AUTHOR CONTRIBUTIONS
All authors contributed to study concept and design. AKH performed the statistical analyses and drafted the manuscript. All authors interpreted the data and critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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