

# BMI–mortality association: shape independent of smoking status but different for chronic lung disease and lung cancer

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**Background:** Besides smoking, low or high body mass index (BMI) is associated with chronic lung disease (CLD). It is unclear how CLD is associated with BMI, whether smoking interacts with this association, and how the associations differ from the patterns known for lung cancer.

**Population and Methods:** Our population comprised 35,212 individuals aged 14–99, who participated in population-based surveys conducted in 1977–1993 in Switzerland (mortality follow-up until 2014). We categorized smokers into never, former, light, and heavy; and BMI into underweight, normal weight, overweight, and obese. Hazard ratios (HRs) were obtained with multivariable Cox proportional hazards models.

**Results:** CLD mortality was strongly associated with being underweight. This was mainly due to the effect in men (HR 5.04 [2.63–9.66]) and also prevailed in never smokers (HR 1.81 [1.11–3.00]). Obesity was also associated with CLD mortality (HR men: 1.37 [1.01–1.86], women: 1.39 [0.90–2.17]), but not with lung cancer mortality. In line with lung cancer, for CLD, the BMI–mortality association followed the same shape in all smoking categories, suggesting that this association was largely independent of smoking status.

**Conclusion:** The shape of the BMI–mortality association was inversely linear for lung cancer but followed a U-shape for CLD. Further research should examine the potentially protective effect of obesity on lung cancer occurrence and the possibly hazardous impact of underweight on CLD development.

**Keywords:** chronic lung disease, lung cancer, mortality, body mass index, underweight, obesity, smoking

## Introduction

Worldwide, COPD was the third and lung cancer the fifth most common cause of death in 2010.<sup>1</sup> While smoking clearly increases the risk of both diseases,<sup>1</sup> the impact of body mass index (BMI) is unclear. For both diseases, higher BMI could be a protective rather than a risk factor, but results are conflicting.<sup>2–10</sup> In underweight individuals, the association between low BMI and disease outcome may be confounded by smoking, because smoking may be more prevalent in underweight than in normal weight people.<sup>7,8,11,12</sup> Moreover, reversed causation may bias the BMI–disease association, because COPD and lung cancer can lead to weight loss.<sup>8</sup> Therefore, smoking and BMI need to be jointly analyzed. In a general population sample from Switzerland, we aim to elaborate similarities and differences regarding associations of BMI and smoking with mortality from chronic lung disease (CLD = mainly COPD) and lung cancer.

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## Materials and methods

### Study population

The study population consists of originally 35,914 individuals aged 14–99 years at baseline who participated in one of four different population-based studies conducted between 1977 and 1993: NRP 1A (National Research Program 1A, 1977–1979, n=8,008); SOMIPOPS (Socio-Medical Indicators for the POPulation of Switzerland, 1982, n=4,104); Swiss MONICA (MONItoring of trends and determinants in CARdiovascular disease, three waves: I, 1984–1986; II, 1988/1989; III, 1992/1993, n=9,940); and the first SHS (Swiss Health Survey, 1992/1993, n=13,862), for details, see the study by Roh et al.<sup>13</sup> The studies were conducted according to the ethical guidelines of the Swiss Academy of Medical Sciences. Informed consent was only obtained for SHS 92/93. For the other studies, the use of written informed consent was not custom when they were conducted, and the ethics committee (Cantonal Ethics Committee of the Canton of Zurich, KEK-ZH) approved our study under these conditions. For details, see the study by Roh et al.<sup>13</sup> Mortality follow-up until 2014 was obtained through anonymous record linkage with the Swiss National Cohort.<sup>13</sup> After exclusion of 30 deceased foreign nationals with missing cause of death, 612 subjects who died of external causes, 1 subject with invalid entry date, and 59 subjects with missing smoking status, our study population comprised 35,212 participants with a median follow-up time of 22.3 years and a maximum of 37.9 years.

### Body mass index

BMI was defined as weight (kg) divided by the square of height (m<sup>2</sup>). Subjects were classified: normal weight ( $18.5 \leq \text{BMI} < 25.0 \text{ kg/m}^2$ ), underweight ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ), overweight ( $25.0 \leq \text{BMI} < 30.0 \text{ kg/m}^2$ ), and obese ( $\text{BMI} \geq 30.0 \text{ kg/m}^2$ ).

### Smoking

Only baseline information was available for smoking status. Smoking was categorized: never, former (reported having ever smoked for >6 months), current light (<20 cigarettes a day), and current heavy ( $\geq 20$ ).

### Covariates

In the final model, we adjusted for age (years), sex, survey (NRP 1A, SOMIPOPS, MONICA I–III, SHS), years of education (number of years: 0–30), marital status (single, married, widowed, divorced), nationality (Swiss vs foreign), self-reported physical activity (four categories:

daily, several times per week, once per week, and less), alcohol consumption (consumption the day before the interview: yes vs no), and a diet proxy (“regularly eating three main meals per day” and “eating fruits and vegetables at least once per day”: yes or no). For all covariates, we used baseline information.

### End points

In view of frequent misclassification<sup>14</sup> and in order to capture all cases potentially related with harmful exposure/behavior, we merged COPD with additional respiratory causes of death into a broader category CLD. As a majority of CLD registrations in Swiss cause of death statistics concerns concomitant causes of death, we included all mentions of CLD. Of these 612 CLD deaths, CLD was mentioned as primary cause of death in 276 death certificates and in 336 as secondary (concomitant) cause. In the latter cases, cardiovascular diseases (55%) were the most frequent primary causes mentioned, followed by cancer (23%). Lung cancer was rarely mentioned as secondary cause of death (1 out of 276 deaths due to CLD), and the definition was, therefore, limited to primary cause of death. Deaths with lung cancer as primary cause and CLD as concomitant were classified as lung cancer. Deaths were coded according to the International Classification of Diseases (ICD-8 until the end of 1994, ICD-10 thereafter). CLD was defined as ICD-8 490–493, 502, 503, 506, 517; ICD-10 J40–J47, J68, J96.1, lung cancer as ICD-8 162; ICD-10 C33–C34.

### Statistical analysis

Death rates were directly age-standardized using the World Health Organization World Standard Population (2000–2025).<sup>15</sup> Testing the proportional hazards assumption, hazard ratios (HRs) for death due to CLD or lung cancer were calculated using Cox proportional hazards regression, where survival times were censored if an individual died because of any other cause of death or was lost to follow-up. We evaluated competing risks regression models,<sup>16</sup> where survival times were censored only due to loss of follow-up but considered competing if the cause of death was not CLD or lung cancer, respectively. The results of the two analysis strategies were essentially the same, so we have reported only results of the Cox proportional hazards models, which some authors (eg, Lau et al<sup>17</sup>) have suggested to be better at answering questions regarding etiology. Analyses were performed with the R programming language (version 3.3.2).

## Results

Baseline characteristics are shown in Table 1. Heavy smokers tended to be male and to be younger than subjects in other smoking categories. They were also less physically active and less likely to have a healthy diet or to be Swiss nationals. CLD-related death was lowest among never smokers (1.0%), intermediate among former and light smokers (2.3% and 2.0%), and highest among heavy smokers (3.1%). However, 4.7% of heavy smokers died due to lung cancer compared to about 1.6% of former or light smokers and only 0.6% of never smokers. The age-standardized death rates were 10.18/1,000 person-years for all causes combined, 0.66 for CLD, and 0.44 for lung cancer (crude: 11.81, 0.76, and 0.69, respectively).

As shown in Figure 1, after full adjustment for covariates, the shape of the association of BMI with CLD and lung cancer mortality was strikingly consistent in smoking status strata. The combined consideration of BMI and smoking categories suggests for lung cancer a quite linear inverse association with the lowest risk in the highest BMI category (obesity). In contrast, the relationship between BMI and CLD

was U-shaped with similarly increased risks in the highest and the lowest BMI category and the lowest risk in normal weight individuals.

## Discussion

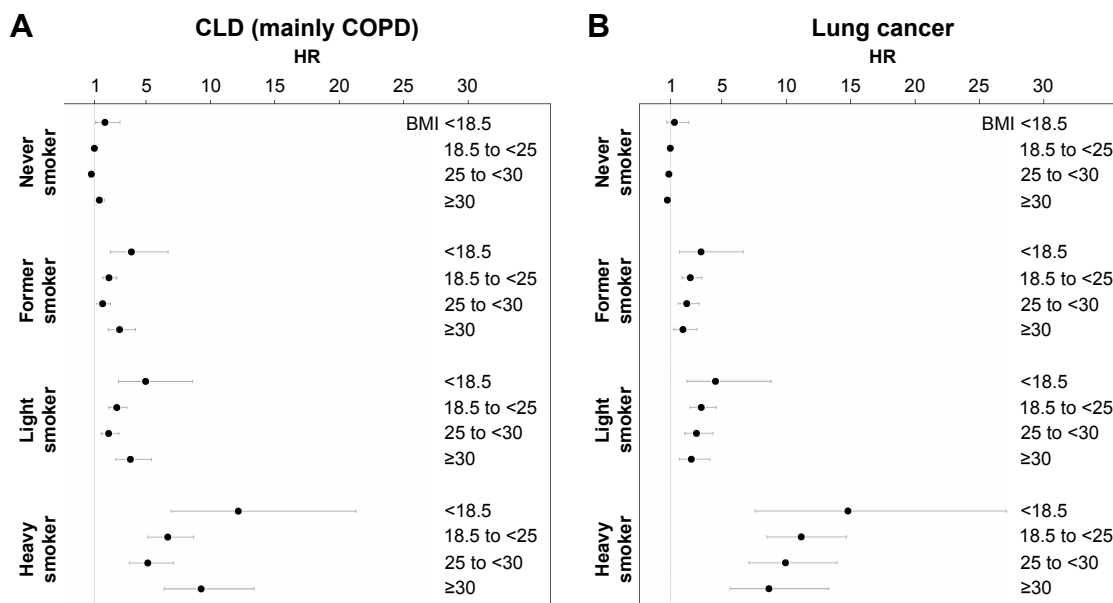
In line with our results, there is a broad agreement regarding the linear inverse association of BMI with lung cancer risk. However, it remains unclear whether the relationship is causal or whether the association is due to reversed causation.<sup>6-9</sup> A study looking at changes in BMI showed that only recent (2 years ago) but not earlier (20 years ago) underweight was associated with increased lung cancer risk and that the strongest predictor for death was a decline in BMI.<sup>8</sup> In contrast to the BMI–lung cancer association, overweight was associated with a lower and obesity with a higher risk of CLD. This U-shaped (vs linear for lung cancer) relationship was also reported in a meta-analysis including more than 10 million individuals.<sup>10</sup> This is at odds with other studies suggesting a lower or a similar risk of CLD among obese compared to normal weight subjects.<sup>2-5</sup> Evidence for an increased CLD mortality risk associated with underweight

**Table 1** Baseline characteristics of the study population

Characteristic	Never	Former	Light	Heavy	Total	Missings <sup>a</sup>
Full dataset <sup>b</sup> (%)	17,028 (47.4)	6,576 (18.3)	7,127 (19.8)	5,123 (14.3)	35,854 (100)	
Analyzed observations, n (%)	16,727 (47.5)	6,468 (18.4)	7,015 (19.9)	5,002 (14.2)	35,212 (100)	702
Women, n (%)	11,124 (66.5)	2,377 (36.8)	3,441 (49.0)	1,685 (33.7)	18,627 (52.9)	0
Person-years	382,060	140,390	166,768	112,246	801,464	
Years of follow-up, mean ± SD	22.8±9.0	21.7±8.9	23.8±9.3	22.4±9.1	22.8±9.1	
Age, mean ± SD	47.0±16.6	48.6±14.7	42.2±14.7	41.2±12.2	45.5±15.6	0
BMI, mean ± SD	24.2±4.0	25.0±4.0	23.8±3.7	24.3±3.8	24.3±3.9	
BMI categories (%)						
< 18.5	637 (3.9)	126 (2.0)	300 (4.3)	165 (3.3)	1,228 (3.5)	443
18.5–25 (ref)	9,817 (59.6)	3,290 (51.4)	4,311 (62.0)	2,887 (58.2)	20,305 (58.4)	
25–30	4,603 (28.0)	2,355 (36.8)	1,927 (27.7)	1,565 (31.6)	10,450 (30.1)	
> 30	1,400 (8.5)	630 (9.8)	412 (5.9)	344 (6.9)	2,786 (8.0)	
Marital status (%)						
Married	10,827 (64.8)	4,909 (75.9)	4,516 (64.4)	3,176 (63.5)	23,428 (66.6)	16
Divorced	809 (4.8)	413 (6.4)	507 (7.2)	549 (11.0)	2,278 (6.5)	
Single	3,594 (21.5)	807 (12.5)	1,712 (24.4)	1,148 (23.0)	7,261 (20.6)	
Widowed	1,490 (8.9)	337 (5.2)	275 (3.9)	127 (2.5)	2,229 (6.3)	
Other covariates						
Alcohol use (%)	9,503 (57.1)	4,823 (74.7)	4,930 (70.5)	3,816 (76.4)	23,072 (65.8)	135
Healthy diet (%)	12,185 (74.0)	4,379 (69.0)	4,456 (64.9)	2,405 (48.2)	23,425 (67.5)	535
Years of education, mean ± SD	11.5±3.2	12.3±3.3	12.0±3.1	11.8±3.1	11.8±3.2	584
Swiss (%)	14,223 (85.0)	5,418 (83.8)	5,693 (81.2)	3,938 (78.7)	29,272 (83.1)	0
Mortality						
All, n (%)	4,524 (27.1)	1,891 (29.2)	1,691 (24.1)	1,359 (27.2)	9,465 (26.9)	
CLD, n (%)	164 (1.0)	150 (2.3)	142 (2.0)	156 (3.1)	612 (1.7)	
Lung cancer, n (%)	95 (0.6)	104 (1.6)	121 (1.7)	236 (4.7)	556 (1.6)	

**Notes:** <sup>a</sup>The maximum number of missing values in an analysis was 2,027 (some individuals had missing values for multiple variables). <sup>b</sup>Excluding 60 study participants with missing information on smoking status.

**Abbreviations:** BMI, body mass index; CLD, chronic lung disease.



**Figure 1** Relative\* risks of chronic lung disease (A) and lung cancer (B) of BMI categories by smoking status (hazard ratios with 95% CI).

**Notes:** \*Reference population are normal weight (BMI 18.5 to  $\leq 25$  kg/m<sup>2</sup>) individuals who never smoked; adjusted for age, sex, survey, years of education, marital status, nationality, physical activity, alcohol consumption, and a diet proxy.

**Abbreviations:** BMI, body mass index; CLD, chronic lung disease; HR, hazard ratio.

is more consistent<sup>2,4,5,10–12,18</sup> and could be observed in people with preexisting lung disease as well as in individuals with normal lung function at baseline.<sup>11,18</sup>

For both CLD and lung cancer, the respective associations between BMI and mortality risk were strikingly similar in all considered smoking status groups. This corroborates other findings, suggesting that the increased CLD risk in underweight individuals is not due to smoking.<sup>3,7,8,11</sup> Partially at odds was a study with a general population sample from Italy, showing that the increased risk of overweight/obesity for COPD was quite independent of smoking status, while in underweight individuals, there was only an increased risk in current and former smokers but not in never smokers.<sup>12</sup> Patients with CLD have an increased energy demand. However, this only holds true for the most progressed form of the disease, and it is very unlikely that such individuals were included in our study. In our population, for both outcomes – CLD and lung cancer – underweight and heavy smoking combined constituted a high risk of death (HR of about 15). Generally, somewhat lower relative risks for this combination were reported.<sup>8,12</sup>

Our study has limitations. The single cross-sectional assessment of risk factors (smoking, BMI) at baseline precludes conclusions regarding causality and temporal sequence. We had data only on mortality and no information on CLD or cancer incidence. The exposure measurement in our study was crude and, for some variables, not uniform as

we pooled different surveys to obtain a sufficient number of deaths. Measurements were only assessed once at baseline precluding the consideration of, for example, smoking status over time. We had no information on objectively measurable mediators of the association between smoking/BMI and death.<sup>19,20</sup> In fact, besides forced expiratory volume, resting heart rate, arm circumference, and other clinical parameters may blunt the impact of BMI on mortality when used in a joint model.<sup>19</sup> The reliability of CLD on death certificates has been questioned.<sup>14</sup> As a consequence, a dilution of the associations might be expected. The close similarity of CLD and lung cancer mortality patterns in our study, however, does not support this concern. We did not consider that causes of death risk competition could vary depending on the length of follow-up time.<sup>21</sup> Younger individuals (eg, aged <40 years) did not notably contribute to CLD death. However, as any limitation of the age range would have been somewhat arbitrary, we decided to analyze the entire available age range.

In conclusion, underweight (for CLD and lung cancer) and obesity (for CLD only) were associated with an increased mortality risk independent of smoking status. Further research is required in order to evaluate the causality of this association and to identify the potential for prevention interventions. Our results stress the need to intensify smoking cessation efforts in people with low or high BMI and – even more importantly – to reinforce public health measures aimed at preventing smoking onset at an early stage of life.



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## Author contributions

DF and MB conceived the study and assisted in data analysis, design of figures and tables, and writing. SRH and MK mainly performed statistical analyses and designed tables and figures. SRH and MK assisted in writing the Materials and Methods section. MB and DF added the important background knowledge and improved the manuscript by repeated readings and rephrasing as well as critical discussions of the intellectual content. All authors critically reviewed the paper and contributed to the final version of the manuscript.

## Disclosure

The authors report no conflicts of interest in this work.

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