Joint Associations of Smoking and Television Viewing Time on Cancer and Cardiovascular Disease Mortality

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Abbreviations: AusDiab, Australian Diabetes, Obesity and Lifestyle Study; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; TV, television.

Article Category: Short Report, Cancer Epidemiology

Novelty and Impact: Sitting time and smoking are both associated with higher risk of cancer and cardiovascular mortality, but their joint associations have not been investigated. This study contributes important information on the joint associations of smoking and television viewing time, showing 23% higher risk of cancer mortality for each additional hour of television time per day, among current-smokers. No association was observed for cardiovascular mortality, or among non-smokers. These findings are hypothesis-generating, and warrant further exploration.

Abstract

Excessive sitting time and smoking are pro-inflammatory lifestyle factors that are associated with both cancer and cardiovascular disease (CVD) mortality. However, their joint associations have not been investigated. We examined the associations of television (TV) viewing time with cancer and CVD mortality, according to smoking status, among 7498 non-smokers (34% ex-smokers) and 1409 current-smokers in the Australian Diabetes, Obesity and Lifestyle Study. During 117,506 person-years (median 13.6 years) of follow-up, there were 346 cancer and 209 CVD-related deaths. Including an interaction between TV time and smoking status in the model significantly improved the goodness of fit for cancer (p=0.01) but not CVD mortality (p=0.053). In the multivariate-adjusted model, every additional h/d of TV time was associated with increased risk of cancer-related (HR 1.23; 95% CI 1.08-1.40), but not CVD-related mortality (HR 1.16; 95% CI 0.97-1.38) in current-smokers. Elevated multivariate-adjusted cancer mortality HRs were observed for current-smokers watching 2 to <4h/d (HR 1.45; 95% CI 0.78-2.71) and ≥4h/d (HR 2.26; 95% CI 1.10-4.64), compared to those watching <2h/d. Current-smokers watching 2 to <4h/d (HR 1.07; 95% CI 0.45-2.53) and ≥4h/d (HR 1.92; 95% CI 0.76-4.84) did not have a significantly higher risk of CVD mortality, compared to <2h/d. No associations were observed for non-smokers. These findings show an association of TV, a common sedentary behavior, with cancer mortality in current-smokers. The association with CVD mortality was less clear. Further exploration in larger data sets is warranted. Limiting TV viewing time may be of benefit in reducing cancer mortality risk in current-smokers.

Introduction

Smoking and sedentary behavior (sitting time) are two of the major lifestyle factors contributing to preventable deaths from non-communicable diseases.[1] Additionally, smoking is a major confounder and effect modifier of chronic disease outcomes associated with lifestyle factors.[2] Chronic inflammation contributes to cancer and cardiovascular disease (CVD) development and progression.[3] Both sedentary behavior and smoking are associated with several key inflammatory markers (C-reactive protein, leptin, interleukin 6 and adiponectin),[3-6] providing a potential mechanistic link to increased cancer and CVD mortality risk. While a few studies have examined the joint associations of sedentary behavior with other lifestyle factors,[7-9] joint associations with smoking have not been investigated. The pro-inflammatory effect of sedentary behavior may interact with carcinogens and other chemicals present in cigarette smoke, and/or disease susceptibility genes, thus modifying associations between smoking and disease outcomes.

We examined the associations of a common sedentary behavior – television viewing (TV) time – with smoking status on cancer and CVD mortality, using data from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. We hypothesized that the magnitude of the association of TV time with cancer and CVD mortality would be greater in current-smokers, due to the multiplicative effect of the chronic inflammation from both exposures.

Materials and Methods

Baseline AusDiab was a population-based study undertaken in 1999/2000 (wave 1; n=11,247 respondents), with longitudinal follow-up in 2004-05 (wave 2; n=8798) and 2011-12 (wave 3; n=6186). The study design, population and measurement of cardiometabolic parameters, including hours per day (h/d) of TV time have been previously described.[10] The

lower response rates in waves 2 and 3 do not impact on the main analyses in this study, as associations have been determined based on baseline risk factors and their impact on mortality outcomes. Total time spent watching TV or videos in the previous 7 days was collected as a continuous variable, using an interviewer-administered questionnaire. This did not include time when the TV was switched on but other activities were being concurrently undertaken. The TV time measure has been shown to provide a reliable (intraclass correlation = 0.82; 95% CI 0.75 to 0.87) and reasonably valid (criterion validity = 0.3) estimate of television time among adults.[11] Three categories of TV time (<2, ≥2 to <4, and ≥4 h/d) were created based on previously identified associations with biomarkers of cardiometabolic risk.[12-14] Changes in TV time were calculated using data from waves 2 and 3. A sensitivity analysis excluded participants whose TV time changed by more than 2 h/d at any time point. Demographic attributes, parental history of diabetes mellitus, smoking, highest level of educational attainment, previous history of CVD (self-reported angina, myocardial infarction, or stroke), and lipid medication use were assessed with interviewer-administered questionnaires. Never-smokers were defined as not currently smoking, and reporting smoking <100 cigarettes over their lifetime; ex-smokers as not currently smoking, and reporting smoking >100 cigarettes over their lifetime or smoking daily in the past; current-smokers as currently smoking daily. Never-smokers (n=4938) and ex-smokers (n=2560) were grouped together as "non-smokers" to increase power for the analyses, as the outcomes in both groups were similar. Self-reported leisure time physical activity (LTPA) was measured by the Active Australia questionnaire, which asks respondents about their participation in predominantly leisure-time exercise during the previous week.[10] Dietary intake (usual eating habits over the past 12 months), total energy intake, and energy intake from alcohol were assessed using self-administered validated food frequency questionnaire.[10] Data were considered valid and included in the analysis if total energy intake was between 500 and 3500 kcal/d for women,

and 800 and 4000 kcal/d for men. Diet quality was assessed with the dietary guideline index (DGI; range 0-130, higher score reflects increased compliance).[15] Oral glucose tolerance tests were performed, and categories of abnormal glucose metabolism were determined according to World Health Organization criteria.[16] Fasting and 2-hour plasma glucose levels, fasting serum triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) levels were obtained by enzymatic methods, measured on an Olympus AU600 analyzer (Olympus Optical, Tokyo, Japan) at a central laboratory. Waist circumference and triplicate resting blood pressures were measured by trained personnel as reported previously.[10] Hypertension was defined as treatment with blood pressure-lowering medication or blood pressure ≥140/90 mmHg. Follow-up was to date of death or November 30, 2013. Mortality status and underlying contributory causes of death (*International Classification of Diseases (ICD)*, 10th revision) were determined by linking the AusDiab cohort to the Australian National Death Index (NDI), the accuracy of which has been established for cancer and CVD mortality.[17, 18] Those who were not matched to the NDI were assumed to be alive. Deaths were attributed to cancer if the underlying and/or contributory causes were coded C00-D48 (*ICD*, 10th revision), and CVD if coded I10-I25, I46.1, I48, I50-I99, or R96. We excluded participants who at baseline reported a history of CVD (coronary heart disease or stroke; n=634), were pregnant (n=60), did not fast for >9 hours (n=25), over-reported or underreported energy intake[10] (n=275), had missing data for variables under consideration (n=1521), or could not be matched to the NDI (n=21); 8907 participants remained in the analysis. Baseline TV time, smoking status and cardiometabolic parameters were used in the main analysis. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) of cancer mortality according to TV time as a continuous measure, and as a categorical variable. Assumptions required for proportional hazards were met. The interaction between baseline TV time and smoking status was assessed by the

likelihood ratio (LR) test of a model that contained the interaction term for TV time and smoking nested within a model not including the interaction term. Sensitivity analyses were undertaken, excluding participants who died in the first two years (n=67), those who changed their TV viewing habits by >2 h/d from baseline (n=746), and cancer deaths without an established link with smoking (n=28; ICD10 codes C55, C56, C73, C795, C833, C835, C900).[19-23] Statistical analyses were performed using Stata V14 (StataCorp LP, Texas, United States of America).

Results

Participant characteristics are presented in Table 1. Relative to <2 h/d of TV time, non-smokers and current-smokers watching ≥4 h/d were older, less likely to have completed 12 years of education, participated in less LTPA, had a lower diet quality, and a more adverse cardiometabolic profile. Over 117,506 person-years (median 13.6 years) of follow-up, 346 cancer-related and 209 CVD-related deaths occurred (Table 2). An association of TV time with CVD, but not cancer mortality, has been previously reported in the AusDiab study.[10] Multivariate-adjusted associations of smoking alone in the current study show an increase in cancer (HR 2.08; 95% CI 1.53-2.82) and CVD (HR 2.92; 95% CI 1.98-4.30) mortality risk for current-smokers compared to non-smokers. Including an interaction between smoking status and TV time in the model significantly improved the goodness of fit for cancer mortality (LR $\chi^2(1)=6.25$, p=0.01), but the relationship did not reach significance for CVD mortality ($\chi^2(1)=3.76$, p=0.053). Further analyses on the association between TV time and cancer mortality were stratified by baseline smoking status. Nested LR tests showed that, in the final model that included LTPA, baseline TV time explained significantly more variation in cancer mortality, compared to the model with LTPA but without TV time, in current-smokers (LR $\chi^2(1)=8.84$, p=0.003), but not in non-smokers (LR $\chi^2(1)=0.35$, p=0.56). In

contrast, in the final model that included LTPA, baseline TV time did not explain more variation in CVD mortality, compared to the model with LTPA but without TV time, in current-smokers or in non-smokers (LR $\chi^2(1)=2.30$, p=0.13; and $\chi^2(1)=0.43$, p=0.51, respectively).

Survival curves for non-smokers and current smokers according to TV time category are presented in Figure 1. Among current-smokers, each additional h/d of TV time was associated with a 23% greater risk of cancer mortality in the multivariate adjusted model (95% CI 1.08-1.40; Table 2). Categorical TV time showed that current-smokers watching ≥4 h/d had a more than 2-fold greater risk of cancer mortality (multivariate-adjusted HR 2.26; 95% CI 1.10-4.64), compared to participants watching <2 h/d. Further adjustment for waist circumference (modelled as a continuous variable) did not attenuate the association between TV time and cancer mortality among current-smokers (Table 2). An exploratory analysis looking at lung cancer specific death in current-smokers showed a non-significant trend toward higher lung cancer mortality risk for every additional hour of TV time per day (multivariate adjusted HR 1.10; 0.87-1.38).

Each additional h/d of TV time was associated with a 27% greater risk of CVD mortality in current-smokers in the minimally-adjusted model (95% CI 1.09-1.48), however this relationship was attenuated in the multivariate-adjusted model (HR 1.16; 95% CI 0.97-1.38). Compared to those watching <2 h/d, current-smokers watching ≥4 h/d of TV had an almost 3-fold greater risk of CVD mortality in the minimally-adjusted model (HR 2.95; 95% CI 1.25-6.98), however this was again attenuated in the multivariate-adjusted model (HR 1.92; 95% CI 0.76-4.84). Greater TV time (continuous or categorical) at baseline was not associated with an increased risk of cancer or CVD mortality among non-smokers (Table 2). A sensitivity analysis with and without adjustment for continuous LTPA had minimal effect on

the association between TV time and CVD or cancer mortality in current-smokers and non-smokers.

A sensitivity analyses excluding participants who died in the first 2 years had minimal effect on the outcomes for non-smokers (57 excluded, 23 cancer deaths, 20 CVD deaths) or current smokers (10 excluded, 1 cancer death, 4 CVD deaths). Additionally excluding participants who changed their TV time habits by >2 h/d also had no effect on the outcomes (621 non-smokers and 125 current-smokers excluded; 11 and 3 cancer deaths, respectively; 9 and 3 CVD deaths, respectively). A sensitivity analysis excluding cancer deaths for sites with no established link with smoking (including brain cancer, ovarian cancer, thyroid cancer, non-Hodgkin lymphoma and multiple myeloma) had no effect on the outcomes for non-smokers (27 cancer deaths excluded) or current-smokers (1 cancer death excluded). Additional adjustment for self-reported number of years as a daily smoker had minimal effect on the observed outcomes. When stratifying by sex, the multivariate-adjusted associations between continuous TV time and cancer mortality were similar for men (HR 1.25; 95% CI 0.99-1.57) and women (HR 1.22; 95% CI 1.01-1.48) current-smokers. Multivariate-adjusted associations for CVD mortality may be higher for men (HR 1.20; 95% CI 0.98-1.46) than for women (HR 0.91; 95% CI 0.53-1.57) current-smokers, though the confidence intervals overlap. No associations were observed for men or women non-smokers.

Discussion

We examined the joint association of TV time and smoking status with cancer and CVD mortality. The findings support our hypothesis that there would be a greater magnitude in the association of TV with cancer outcomes in current-smokers, in comparison to non-smokers. However, this does not appear to be due to a multiplicative effect as no association was observed for non-smokers. Lung cancer has one of the highest incidence rates of all cancers,

especially amongst smokers. Of the 60 cancer deaths in current-smokers, 26 (44%) were from lung cancer, and an exploratory analysis showed a non-significant trend toward higher cancer mortality risk for every additional hour of TV time per day. The relationship between TV time and CVD outcomes in current-smokers was less clear, as the association was attenuated in the multivariate-adjusted model. Recently, sedentary behaviors have been linked to increased cancer and CVD incidence and mortality risk, including a number of studies which have controlled for smoking status.[9, 24] The underlying mechanisms leading to the associations observed in our study could include inflammation, whereby the pro-inflammatory effect of sedentary behavior[4-6] may interact with carcinogens and other chemicals present in cigarette smoke, and/or disease susceptibility genes, to modify the associations between smoking and diseases such as cancer and CVD.

The absence of a significant effect in non-smokers could be due to lack of power to observe significant effects, as the hazard ratio for cancer and CVD mortality with increasing TV time may be quite small in this population, compared to current smokers. Alternatively, there may be no association between TV time and cancer or CVD mortality in non-smokers. Despite the current results, others have demonstrated that never-smokers and ex-smokers with high daily sitting or TV time are at greater risk of all-cause[7] and inflammatory-related mortality (excluding cancer and cardiovascular disease mortality),[25] suggesting that non-smokers may exhibit greater risk of other causes of mortality.

Strengths of our study include the recruitment of a national sample of participants across a wide age range. Limitations include the small number of deaths, particularly in the current-smoker cohort. Small sample size may have limited our ability to observe a significant interaction between TV time and smoking for CVD mortality, and effects in the categorical TV time analysis. Never-smokers and ex-smokers were grouped together as “non-smokers” to increase power for the analyses, as the outcomes in the two groups were similar. However,

deleterious effects for cancer and CVD mortality have previously been reported for ex-smokers, suggesting that these two groups should be separated in future studies with a larger sample size. The analyses were based on self-report assessment of a single sedentary behavior (TV time), and current and prior smoking behaviors. The associations of TV time with CVD and cancer mortality did not change when adjusting for self-reported number of years as a daily smoker. However, we cannot exclude additional effects of residual confounding by smoking. Adjustment for waist circumference also did not attenuate the associations of TV time with CVD or cancer mortality. Waist circumference could be a confounder or a mediator in the pathway for TV time. The association is likely bidirectional, where long time spent watching television may lead to obesity, and obesity may lead to a propensity to watch greater amounts of television. Future studies should consider this relationship. Baseline self-reported cancer was not measured, therefore, these participants could not be excluded. However, we performed a sensitivity analysis excluded deaths occurring in the first 2 years to try and address reverse causation.

The results of this study are intended to be hypothesis-generating; further exploration in a dataset with greater numbers of deaths and longer-term follow-up is warranted. Concurrent assessment of various inflammatory markers would help to determine whether inflammation is a contributor to the joint association between sedentary behavior and smoking on risk of cancer and CVD mortality. More accurate assessment of smoking status incorporating lifetime tobacco consumption (e.g. pack-years) and time since quitting could be incorporated into future analyses to improve the power of future studies to observe significant effects. Objective assessment of sedentary behaviors, in various domains (e.g. home, work and travel) would also provide more accurate and context-specific information on the added risks of high levels of sedentary time in addition to smoking status.

In conclusion, our findings showed a common sedentary behavior to be positively associated with cancer mortality in current-smokers. However, an association with CVD mortality was less clear. We postulate that the underlying mechanisms could be linked to increased basal inflammation.

Figure Legend

Figure 1. Unadjusted cumulative hazard estimates according to TV viewing time categories. Cancer mortality for (A) non-smokers and (B) current-smokers; and CVD mortality for (C) non-smokers and (D) current-smokers.

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Table 1. Baseline characteristics, according to smoking status and average hours per day spent watching television

	Non-Smokers			Current-Smokers		
	TV Viewing Time, h/d			TV Viewing Time, h/d		
	<2	2 to <4	≥4	<2	2 to <4	≥4
Total, n (%)	4329 (58)	2663 (36)	506 (7)	699 (50)	532 (38)	178 (13)
Men, n (%)	1792 (42)	1235 (46)	234 (46)	302 (43)	287 (54)	99 (56)
Age, y	49.0 (12.9)	53.5 (14.5)	59.3 (14.9)	44.5 (11.0)	45.5 (12.0)	48.4 (14.0)
Education ≥12 y, n (%)	2945 (68)	1483 (56)	226 (45)	401 (57)	287 (54)	75 (42)
Lifestyle variables						
Energy Intake (total), kJ/d	7451 (5848-9302)	7548 (5930-9494)	7406 (5867-9448)	7604 (6142-9615)	7829 (6052-10119)	8386 (5992-10993)
Energy Intake (alcohol), kJ/d	205 (28-601)	181 (19-614)	72 (4-419)	375 (54-1030)	415 (50-1080)	194 (16-807)
Dietary Guideline Index, %	86.0 (13.7)	84.6 (14.0)	84.1 (14.2)	76.1 (14.3)	74.5 (13.6)	74.5 (13.7)
Household Income ≥$400/wk	2727 (63)	1355 (51)	166 (33)	392 (56)	281 (53)	52 (29)
Television viewing time, h/d	0.93 (0.53)	2.58 (0.53)	4.85 (1.08)	0.93 (0.56)	2.67 (0.56)	5.40 (1.96)
LTPA time, h/d*	0.68 (0.79)	0.66 (0.80)	0.57 (0.71)	0.66 (0.86)	0.60 (0.76)	0.50 (0.71)
Medical history/conditions, n (%)						
Hypertension†	1127 (26)	999 (38)	251 (50)	117 (17)	116 (22)	46 (26)
Lipid medication use	209 (5)	243 (9)	74 (15)	25 (4)	34 (6)	15 (8)

Diagnosed diabetes mellitus‡	96 (2)	105 (4)	41 (8)	14 (2)	21 (4)	7 (4)
Diagnosed diabetes mellitus >10 y‡	24 (1)	24 (1)	15 (3)	5 (1)	4 (1)	2 (1)
Cardiometabolic variables						
Body mass index, kg/m^2	26.5 (4.8)	27.3 (4.9)	28.9 (5.6)	26.0 (4.6)	26.7 (4.8)	27.0 (5.5)
Waist circumference, cm	88.6 (13.6)	92.2 (13.4)	96.9 (14.5)	88.7 (13.6)	91.6 (13.6)	93.4 (14.4)
Systolic BP, mm Hg	127.1 (17.7)	132.0 (18.9)	137.0 (19.0)	122.0 (15.6)	125.6 (16.6)	124.9 (18.9)
Diastolic BP, mm Hg	69.8 (11.7)	70.7 (11.6)	72.0 (11.9)	67.5 (11.0)	69.2 (12.2)	68.8 (11.8)
Total cholesterol, mmol/L	5.57 (1.02)	5.76 (1.08)	5.87 (1.06)	5.63 (1.10)	5.73 (1.14)	5.83 (1.12)
HDL-C, mmol/L	1.47 (0.39)	1.42 (0.37)	1.40 (0.37)	1.39 (0.37)	1.34 (0.36)	1.30 (0.37)
Triglycerides, mmol/L§	1.14 (0.80-1.70)	1.33 (0.93-1.94)	1.51 (1.05-2.19)	1.25 (0.90-1.86)	1.42 (0.99-2.23)	1.60 (1.10-2.35)
Fasting plasma glucose, mmol/L§	5.5 (1.0)	5.6 (1.1)	5.9 (1.7)	5.4 (1.1)	5.7 (1.3)	5.6 (1.0)
2-h plasma glucose, mmol/L§	5.7 (4.8-6.8)	6.0 (5.1-7.3)	6.9 (5.5-8.3)	5.3 (4.5-6.3)	5.5 (4.5-6.6)	5.7 (4.9-7.5)

Data are mean (SD) where appropriate.

*Leisure time physical activity (LTPA) was measured by the Active Australia questionnaire, which asks respondents about their participation in predominantly leisure-time exercise.

†Hypertension defined as blood pressure ≥140/90 mm Hg or taking antihypertensive medication

‡Diagnosed diabetes mellitus based on self-reported hypoglycaemic medication use, a fasting plasma glucose ≥7.0 mmol/L, or a 2-hour plasma glucose level of ≥11.1 mmol/L

§Data are median (25th to 75th percentiles)

Table 2. Risk of Cancer and CVD mortality according to smoking status and hours per day spent watching television

	Continuous Television Viewing Time, h/d	Categorical Television Viewing Time, h/d			
		<2	≥2 to <4	≥4	*P* for Linear Trend
Cancer Mortality					
Non-Smokers					
Cancer deaths, n	287	135	118	34	
Age and sex-adjusted HR (95% CI)	1.00 (0.91-1.09)	Reference	0.94 (0.73-1.20)	0.98 (0.67-1.43)	0.74
Multivariate-adjusted HR (95% CI)*	0.97 (0.89-1.06)	Reference	0.92 (0.72-1.19)	0.90 (0.61-1.33)	0.51
Multivariate and waist circumference adjusted HR (95% CI)*	0.97 (0.89-1.06)	Reference	0.92 (0.72-1.19)	0.91 (0.61-1.34)	0.52
Current-Smokers					
Cancer deaths, n	59	20	23	16	
Age and sex-adjusted HR (95% CI)	**1.25 (1.11-1.41)**	Reference	1.29 (0.70-2.36)	**2.35 (1.20-4.60)**	**0.02**
Multivariate-adjusted HR (95% CI)*	**1.23 (1.08-1.40)**	Reference	1.45 (0.78-2.71)	**2.26 (1.10-4.64)**	**0.02**
Multivariate and waist circumference	**1.23 (1.08-1.41)**	Reference	1.44 (0.77-2.69)	**2.27 (1.11-4.67)**	**0.02**

adjusted HR (95% CI)*					
CVD Mortality					
Non-Smokers					
CVD deaths, n	209	81	94	34	
Age and sex-adjusted HR (95% CI)	1.00 (0.97-1.10)	Reference	0.99 (0.73-1.33)	1.19 (0.79-1.78)	0.52
Multivariate-adjusted HR (95% CI)*	0.97 (0.87-1.07)	Reference	0.94 (0.69-1.27)	1.03 (0.68-1.55)	0.99
Multivariate and waist circumference adjusted HR (95% CI)*	0.97 (0.88-1.07)	Reference	0.93 (0.69-1.26)	1.04 (0.69-1.57)	0.99
Current-Smokers					
CVD deaths, n	38	10	16	12	
Age and sex-adjusted HR (95% CI)	**1.27 (1.09-1.48)**	Reference	1.48 (0.66-3.30)	**2.95 (1.25-6.98)**	**0.02**
Multivariate-adjusted HR (95% CI)*	1.16 (0.97-1.38)	Reference	1.07 (0.45-2.53)	1.92 (0.76-4.84)	0.19
Multivariate and waist circumference adjusted HR (95% CI)*	1.14 (0.97-1.35)	Reference	1.11 (0.46-2.63)	2.02 (0.80-5.12)	0.16

*Multivariate models are adjusted for age, sex, leisure time physical activity, education (≥12 years), household income, total energy intake, alcohol intake, Dietary Guideline Index[19], hypertension (blood pressure ≥140/90 mm Hg or antihypertensive medication use), total plasma cholesterol (mmol/L), HDL-C (mmol/L), serum triglycerides (mmol/L, log), lipid-lowering medication use, and glucose tolerance status (impaired fasting glucose, impaired glucose tolerance, undiagnosed diabetes mellitus, known diabetes mellitus according to 1999 World Health Organization criteria[20]).

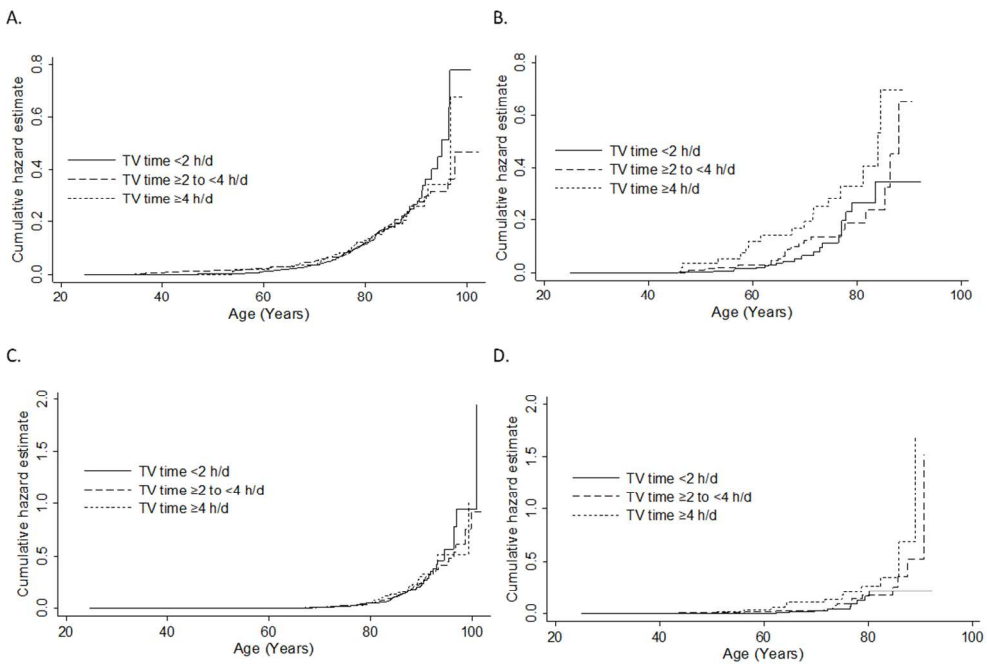

Figure 1. Unadjusted cumulative hazard estimates according to TV viewing time categories. Cancer mortality for (A) non-smokers and (B) current-smokers; and CVD mortality for (C) non-smokers and (D) current-smokers.

195x133mm (150 x 150 DPI)