Prospective association of TV viewing with acute phase reactants and coagulation markers: English Longitudinal Study of Ageing

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Abstract

Objective: Inflammatory processes are putative mechanisms underlying the detrimental health effects of sedentary behaviour but no long-term prospective data are available. We examined the longitudinal association between TV viewing, physical activity and inflammatory markers over a 4-year follow-up period.

Methods: Participants were 3612 men and women (mean age 64.1±8.2 years) from the English Longitudinal Study of Ageing. Self-reported daily TV viewing was measured at baseline and 2 years follow up. Inflammatory markers (serum high-sensitivity C-reactive protein [CRP], white blood cell count [WBC], and fibrinogen) were measured at baseline (2008/09) and 4 years follow-up (2012/13).

Results: On average, participants viewed TV for 5.1± 4.0 hrs/d, and there was an increase of 1.9 hr/wk TV viewing over 2 years. In linear models adjusted for covariates including physical activity, TV viewing was not associated with $\log_e$CRP at follow-up (B=0.004, 95% CI, -0.001, 0.009, p=0.09) but was associated with WBC (B=0.018, 95% CI, 0.005, 0.031, p=0.006), and fibrinogen (B=0.004, 95% CI, 0.00, 0.008, p=0.035). In contrast, physical activity was inversely associated with CRP (p=0.047) and WBC (p=0.026), but not fibrinogen (p=0.22). An increase in TV viewing (of at least 1 hr/d) was associated with higher concentrations of CRP (p=0.015) and WBC (p=0.05) at follow up after adjustment for covariates and baseline TV viewing.

Conclusions: Physical activity and sedentary behaviour have contrasting associations with markers of low grade inflammation over 4 years of follow-up. These behaviors may be important in influencing the pro-inflammatory state seen with ageing.

Key words: Adiposity; Blood Coagulation; Exercise; Inflammation; Sedentary Lifestyle

Introduction

Pro-inflammatory status appears to increase with age, that may underlie biological mechanisms responsible for cardiovascular disease (CVD) and other age-related diseases.[1-4] Physical activity may have beneficial anti-inflammatory effects as evidence from epidemiological studies has consistently demonstrated an inverse association between physical activity and markers of low grade systemic inflammation.[5-7] The anti-inflammatory effects of exercise may partly explain the well-documented cardio-protective effects of physical activity.[8-10] In contrast, little is known about the association between sedentary behaviours and low grade inflammation.

Sedentary behaviour has been conceptualised as a distinct domain of behaviour, which may pose a risk to health independently of physical activity.[11] Sedentary behaviour has been consistently associated with risk of CVD in population cohort studies, [12-15] although the mechanisms remain poorly understood. Television (TV) viewing is a major component of leisure sedentary time[16], particularly in older adults[17] and is distinct from other sedentary behaviours in that it is passive and encourages prolonged periods of sitting. Moreover, TV viewing is likely to influence other behaviour, for example, dietary habits by encouraging an increased consumption of energy-dense food.[18] Thus, it remains unknown if excess TV viewing is simply a marker of energy imbalance and other confounding or if results are driven by actual postural effects (ie, prolonged sitting).

Several studies have demonstrated cross-sectional associations between TV viewing or objective sedentary time with markers of low grade inflammation.[19-22] However, there are a paucity of longitudinal data. We recently demonstrated an association between TV viewing

(aged 23) and inflammatory markers at follow up (aged 44) in a birth cohort study but were unable to infer true changes over time since biomarkers were not collected at baseline.[23]

The aim of this study was therefore to examine longitudinal associations between TV viewing, physical activity and inflammatory markers over a 4-year follow-up period in a cohort of older adults. Uniquely, we also explored associations between changes in TV viewing on subsequent inflammatory markers.

Materials and Methods

Study sample and procedures

The English Longitudinal Study of Ageing (ELSA) was initiated in 2002 containing a nationally representative sample of the English population living in households.[24] The ELSA cohort consists of men and women born on or before 29 February 1952. Multistage stratified probability sampling was used to select the sample with postcode sectors selected at the first stage and household addresses selected at the second stage. For the purposes of the present analyses, data collected at wave 4 (2008/9) were used as the baseline as this was the first occasion information on TV viewing was gathered. Clinical information was gathered by nurses in participants' homes at wave 4 and at follow-up (wave 6; 2012/13). In addition, data on TV viewing was also collected at wave 5 (2010/11). Participants gave full informed written consent to participate in the study. Ethical approval was obtained from the London Multi-center Research Ethics Committee, compliant with the Declaration of Helsinki.

Baseline TV viewing and physical activity

At waves 4 and 5 participants were asked to recall “How many hours of television do you watch on an ordinary day or evening, that is, Monday to Friday” and “How many hours of television do you normally watch in total over the weekend, that is, Saturday and Sunday.” Average daily time spent watching TV was calculated as {(weekday TV time x 5) + (Weekend TV time)}/7. We calculated the 2 year change in TV viewing by subtracting total reported weekly TV viewing hours at wave 5 from wave 4.

Participants were asked three questions regarding how often they took part in vigorous, moderate- and low-intensity physical activity, using prompt cards with different activities to help them interpret physical activity intensities. Response options for each question were: more than once a week, once a week, one to three times a month and hardly ever/never. Physical activity was then categorised as: inactive (participants that reported no moderate or vigorous activity at least once a week); moderate activity at least once a week (but no vigorous); vigorous activity at least once a week. The physical activity and TV viewing measures used in ELSA have demonstrated excellent convergent validity in grading a plethora of psychosocial, physical and biochemical risk factors in previous work.[25-28]

Clinical assessments

Nurses collected anthropometric data (weight, height), and blood samples. Participants’ body weight was measured using Tanita electronic scales without shoes and in light clothing, and height was measured using a Stadiometer with the Frankfort plane in the horizontal position. Body mass index (BMI) was calculated using the standard formulae [weight (kilograms)/height (meters) squared]. Blood samples were analyzed for several inflammatory marker categories, including acute phase reactants (high sensitivity C-reactive

protein [CRP], white blood cell count [WBC]) and coagulation products (fibrinogen). Blood analysis was carried out at the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK). Detailed information on the technicalities of the blood analysis, the internal quality control, and the external quality assessment for the laboratory have been described elsewhere.[29]

Covariates

Trained interviewers asked questions on cigarette smoking (current or non-smoker), alcohol intake (categorised as; at least five times a week, at least once a week, monthly, rarely/never), use of prescribed medication (including medication for diabetes, high blood pressure, cholesterol, blood thinning), chronic illness, and depressive symptoms (using the 8-item Centre of Epidemiological Studies Depression scale[30]). Disability was assessed based on participants' responses to interviewer questions on perceived difficulties in six basic activities (e.g. difficulty dressing) and seven instrumental activities of daily living (e.g. difficulty preparing a hot meal).[31] Participants reporting difficulties in one or more activities were considered to have some degree of disability.

Statistical analyses

Characteristics of the study population at baseline were described as categorical variables. Log transformations were used to normalise the distribution of CRP. We examined prospective associations between baseline TV and inflammatory markers (CRP, WBC, and fibrinogen) using linear regression models with TV time entered as a continuous independent variable. We tested for interactions with sex but none were noted. The models were adjusted for age, sex, baseline concentration of inflammatory marker, smoking, alcohol, medications, depressive symptoms, long standing illness, disability, body mass

index, and physical activity. These covariates were selected a priori based on previous literature.[7,17,23,26] Similar models were run to examine the association between physical activity and inflammatory markers. In order to assess the association between changes in TV viewing on inflammatory markers we generated three categories (stable; reduction of at least 1 hr/d; increase of at least 1 hr/d). A change in 1hr/d TV was chosen as it roughly reflected the top and bottom quarter of the distribution. Using dummy variables (with the stable group designated as the referent category), TV change was regressed onto inflammatory markers at follow up, using the same covariates described above. All analyses were conducted using SPSS version 21.

Results

A sample size of 5463 provided complete baseline data although 1851 participants were lost to follow-up leaving a final analytic sample of 3612. Compared with the analytic sample, those lost to follow-up were slightly older (64.1 vs. 65.9 yrs, p= 0.001), had higher baseline logCRP concentration (1.15 vs. 1.22, p=0.001), higher baseline TV viewing (5.1 vs. 5.5 hr/d, p=0.001), although there were no differences in sex distribution (% men; 45.0 vs 45.9, p=0.53) or body mass index (28.0 vs. 28.2 kg/m^2, p= 0.09). A further 83 and 158 participants had missing data on WBC and fibrinogen, respectively, thus slightly different sample sizes were used in analysis of different inflammatory markers.

The baseline characteristics of the sample are shown in Table 1. High levels of TV viewing (>6 hr/d) were reported in 26.4% of participants and 15.0% of the sample reported no weekly physical activity of at least moderate intensity. Obesity was prevalent in 28.3% and clinically elevated CRP was observed in 31.2% of the sample.

Between baseline and follow-up, there was a small reduction in CRP (median [interquartile range]; 1.80 [2.88] vs. 1.50 [2.30] mg/L, p=0.001) and fibrinogen (mean ± SD; 3.33 ± 0.54 vs. 2.96 ± 0.52 g/L, p=0.001) but an increase in WBC (mean ± SD; 6.29 ± 2.0 vs. 6.42 ± 1.94 10^9cells/L, p=0.001). In models adjusted for age, sex, and baseline CRP, both TV viewing and physical activity were associated with logCRP at 4 years follow up (Table 2). In final adjusted models, only physical activity remained (inversely) associated with logCRP (p=0.047). Both TV viewing (p=0.006) and physical activity (p=0.026) remained associated with WBC in final adjusted models (Table 2). TV viewing remained associated with fibrinogen in final adjusted models (p=0.035) although physical activity did not (p=0.22) (Table 2). The results remained unchanged when we adjusted for waist circumference instead of BMI. For example, in final adjusted models TV viewing was not associated with $\log_e$CRP (p=0.08) but was associated with WBC (p=0.016), and fibrinogen (p=0.020). In order to identify if one covariate in particular attenuated the effect estimates we added both BMI and physical activity separately into Model 1 before other covariates. However, this strategy caused minimal changes to the effect estimate leading us to conclude that possible confounding influences were explained evenly across all covariates, and not by one in particular.

We performed several sensitivity analyses. First, to explore possible reverse causation we removed participants (n=802) that reported any cardiovascular diseases (angina, myocardial infarction, congestive heart failure, heart murmur, arrythmia) over the first four waves of ELSA. The results for TV viewing were unchanged in final adjusted models; CRP (B=0.004, 95% CI, -0.002, 0.009; p=0.17), WBC (B=0.016, 95% CI, 0.003, 0.030; p=0.019), fibrinogen (B=0.004, 95% CI, 0.000, 0.008; p=0.06). Second, we performed analyses to explore the

possible additive effects of physical activity and TV viewing. Participants were split into four groups based on combinations of high/low physical activity (vigorous at least once a week) and high/low TV (4hr/d cut off point). In high TV viewers, no differences were observed for any inflammatory markers between high or low physical activity groups. However, Active/high TV viewers demonstrated higher WBC compared to Active/ low TV viewers (adjusted B=0.23, 95% CI, 0.05, 0.40; p= 0.01), presented in figure S1.

On average there was an increase of 1.9 hr/wk (SD, 31.5) TV viewing over 2 years. Approximately half of the sample (53.2%) remained relatively stable (less than 1 hr/d change), whilst 20.6% reported a substantial reduction of more than 1 hr/d and 26.2% an increase of more than 1 hr/d in TV viewing. An increase in TV viewing was associated with higher concentrations of CRP (p=0.015) and WBC (p=0.05) at follow up after adjustment for covariates and baseline TV viewing (Table 3).

Discussion

The aim of this study was to examine longitudinal associations between TV viewing (a major component of sedentary behaviour) and a range of inflammatory markers. Inflammatory processes are putative mechanisms underlying the detrimental health effects of sedentary behaviour but little long-term prospective data are available. We demonstrated an association between TV viewing and increased WBC (acute phase reactant) and fibrinogen (coagulation product) concentration at follow-up after adjustment for a range of clinical and behavioural covariates. In addition, an increase in TV viewing was associated with elevated CRP and WBC at follow up.

Several studies have previously demonstrated cross-sectional associations between TV viewing and markers of low grade inflammation.[19,20] For example, in over 3,000 Australian adults TV time was associated with CRP and fibrinogen although after adjustment for waist circumference these relationships were attenuated to the null.[19] In a small study of 285 adults, changes in sedentary time over 6 months were associated with CRP in women, although no associations were observed with other biomarkers, including adiponectin, soluble intracellular adhesion molecule-1, and interleukin-6.[32] In a longitudinal cohort study baseline TV viewing time was not significantly associated with change in metabolic biomarkers over 5 years follow-up although inflammatory markers were not examined.[33] Nevertheless, increases in TV time over 5 years were associated with increases in waist circumference, diastolic blood pressure, and a clustered cardiometabolic risk score. In a British birth cohort study we demonstrated an association of TV viewing (aged 23) with CRP and fibrinogen at follow-up (aged 44),[23] although the effect estimates were attenuated after adjustments for BMI, especially so in participants with a BMI ≥ 25 kg/m^2. This is the first study to show associations between changes in TV viewing and inflammatory markers. Unlike previous work, our results were not largely attenuated by the inclusion of BMI or waist in the models. This is possibly explained by the older age of the present sample ; particularly in an elderly sample with onset of sarcopenia measures such as BMI are less reflective of adiposity.

Sedentary behaviours such as TV viewing are characterised by a lack of muscle contraction. Thus, the association between TV viewing and low grade inflammation is plausible since muscle contraction has been shown to stimulate the expression of various transcriptional co-activators such as PGC1α, which lead to a transient release of myokines that may

promote systemic anti-inflammatory effects.[34] Other research has demonstrated that prolonged sitting is associated with the expression of various genes linked to inflammatory responses.[35] Adipose tissue inflammation might also explain links between sedentary behaviour and inflammation.[36] Indeed, reductions in central adiposity largely explain the changes in CRP observed after aerobic exercise training interventions.[37,38] Thus, excess TV viewing may simply be a marker of chronic energy imbalance indicated by excess adiposity. We have recently demonstrated associations between objectively assessed sitting time and visceral adiposity, including liver fat,[39] which is believed to be a particularly important site for the production of pro-inflammatory markers.[40]

The association between TV viewing and fibrinogen may also have relevance in terms of elevated risk of vascular conditions, particularly venous thrombosis. Our results support findings from a recent experimental trial that demonstrated increases in plasma fibrinogen with prolonged uninterrupted sitting that was attenuated with active breaks.[41] Some epidemiological studies have demonstrated that associations between sedentary behaviour and CVD are attenuated in physically active participants.[14,15] However, in our analysis to explore the possible additive effects of physical activity and TV viewing on inflammatory markers we did not observe any significant effect modification of physical activity (see figure S1). Physical activity was, however, rather crudely defined (vigorous activity at least once a week), thus future experimental studies are needed to define the dose of activity required to attenuate deleterious effects of prolonged sitting.

Our study has some notable strengths, including the longitudinal design to examine changes in TV time and biomarkers across 4 years; the use of a large national sample of community-dwelling men and women; and the inclusion of a wide range of potentially important

factors, including behavioral, social and clinical covariates. There are also some limitations. Our measure of sedentary behavior was limited to TV viewing thus our results cannot be generalized to total sedentary time or sitting. The questionnaires used to assess TV viewing in ELSA have not been validated and may have introduced an element of recall bias. Nevertheless, the TV measure has demonstrated excellent convergent validity in grading a plethora of psychosocial, physical and biochemical risk factors in previous work.[26,27] Also, sedentary time questions that focus on TV viewing have demonstrated the strongest reliability and validity among non-occupational sedentary behaviour questions.[42] It was not possible to adjust models for diet, as such data were not collected. However, recent data has suggested that snack food and TV viewing were independently associated with metabolic syndrome.[43] The analytic sample differed in some characteristics compared with those excluded that reduces the representativeness of our data. In particular, those excluded were slightly older and watched higher amounts of TV, thus the results may reflect a conservative estimate of the true associations. The stability of markers such as CRP over long term follow-up has been found to be similar to that of blood pressure and serum cholesterol,[44] which makes it suitable for use in risk prediction studies. Surprisingly, we observed slight reductions in two inflammatory markers over the 4 year follow-up period, although this might be accounted for by use of medication since 20.3% of the sample reported taking statins at baseline known to have anti-inflammatory properties.[45]

In summary, TV viewing was associated with increased WBC and fibrinogen, but not CRP, over 4 years follow-up. For the first time, we show associations between changes in TV viewing and elevated inflammatory markers. Sedentary behaviours may be important in influencing the pro-inflammatory state seen with ageing.

Author contributions

M Hamer had full access to the data, and takes responsibility for the integrity and accuracy of the results. M Hamer drafted the paper, performed analyses and designed the study.
L Smith contributed to the concept and design of the study and critical revision of the manuscript.
E Stamatakis contributed to the concept and design of the study and critical revision of the manuscript.

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Conflict of interest

None of the authors have any competing interests to declare.

Data sharing statement

Full ELSA data are available at the UK data archive http://www.data-archive.ac.uk/ .

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Table 1. Descriptive characteristics of the sample at baseline (n=3612)

Variable	N (%)
Age category	
50 – 59	1170 (32.4)
60 – 69	1495 (41.4)
70 – 79	784 (21.7)
≥80	163 (4.5)
Sex	
Men	1626 (45.0)
Women	1986 (55.0)
TV viewing	
< 2hr/d	415 (11.5)
2 < 4 hr/d	1286 (35.6)
4 < 6 hr/d	957 (26.5)
≥ 6 hr/d	954 (26.4)
Physical activity	
Inactive	541 (15.0)
Moderate at least 1/wk	1809 (50.1)
Vigorous at least 1/wk	1262 (34.9)
Body mass index category	
15 < 25 kg/m^2	1006 (27.9)
25 < 30 kg/m^2	1584 (43.9)
≥ 30 kg/m^2	1022 (28.3)
Smoking	
None	3182 (88.1)
Current	430 (11.9)
Alcohol intake	
At least 5 times a week	857 (23.7)
at least once a week	1512 (41.9)
monthly	663 (18.4)
Rarely/never	580 (16.1)
Depressive symptoms	
CES-D score 0 – 3	3230 (89.4)
CES-D score ≥ 4	382 (10.6)
Disabilities	
None	2930 (81.1)
At least one	682 (18.9)
Longstanding illness	
None	1805 (50.0)
Any	1807 (50.0)
Medications†	
No	2233 (61.8)
Yes	1379 (38.2)
C-reactive protein category	
< 1 mg/L	1037 (28.7)
1 < 3 mg/L	1447 (40.1)
≥ 3 mg/L	1128 (31.2)

† including medication for diabetes, high blood pressure, cholesterol, blood thinning

Table 2. Linear regression analyses of TV viewing and physical activity on inflammatory markers at 4 years follow-up.

Baseline independent variable	**Model 1 B (95% CIs)**	**Model 2 B (95% CIs)**	**Model 3 B (95% CIs)**
Log_e C-reactive protein (N=3612)			
TV viewing	0.007 (0.002, 0.012)*	0.004 (0.00, 0.009)*	0.004 (-0.001, 0.009)
Physical activity	-0.058 (-0.087, -0.029)*	-0.032 (-0.062, -0.002)*	-0.031 (-0.061, 0.000)*
White blood cell count (N=3529)			
TV viewing	0.027 (0.014, 0.040)*	0.019 (0.006, 0.032)*	0.018 (0.005, 0.031)*
Physical activity	-0.17 (-0.25, -0.092)*	-0.099 (-0.18, -0.018)*	-0.092 (-0.17, -0.011)*
Fibrinogen (N=3454)			
TV viewing	0.006 (0.003, 0.010)*	0.004 (0.00, 0.008)*	0.004 (0.00, 0.008)*
Physical activity	-0.036 (-0.058, -0.014)*	-0.016 (-0.039, 0.007)	-0.015 (-0.038, 0.009)

B reflects unstandardised coefficient for inflammatory marker. *p<0.05

Model 1: adjusted for age, sex, inflammatory marker at baseline (CRP, or WBC, or fibrinogen).
Model 2: adjusted for age, sex, inflammatory marker at baseline, smoking, alcohol, depressive symptoms, long standing illness, disability (ADLs/IADLs), medications, body mass index.
Model 3: adjusted for all covariates in model 2 + mutually for TV time or physical activity.

Table 3. Regression of change in TV viewing on inflammatory markers at follow-up.

	Reduced TV viewing	**Stable**	**Increased TV viewing**
Log_e C-reactive protein			
Model 1	0.06 (-0.03, 0.13)	Reference	0.10 (0.05, 0.16)*
Model 2	0.07 (-0.01, 0.14)	Reference	0.07 (0.01, 0.12)*
White blood cell count			
Model 1	-0.013 (-0.22, 0.19)	Reference	0.24 (0.09, 0.39)*
Model 2	0.06 (-0.14, 0.25)	Reference	0.15 (0.00, 0.30)*
Fibrinogen			
Model 1	0.03 (-0.02, 0.09)	Reference	0.05 (0.01, 0.10)*
Model 2	0.05 (-0.01, 0.10)	Reference	0.03 (-0.01, 0.07)

Data reflect unstandardised coefficient for inflammatory marker. *p<0.05

Model 1: adjusted for age, sex, baseline TV time.
Model 2: adjusted for age, sex, baseline TV time, smoking, alcohol, depressive symptoms, long standing illness, disability (ADLs/IADLs), medications, body mass index, physical activity.