Physical activity, morbidity and mortality in twins: a 24-year prospective follow-up

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Abstract

The aim of this study was to find out whether persistent leisure-time physical activity, adjusted for genetic liability and childhood experiences, protect against occurrence of specific chronic diseases and all-cause mortality. Study design was a 24-year prospective follow-up after 6-year physical activity discordance in twin pairs. From 5663 healthy adult twin pairs, 146 pairs (including 29 mozygotic) discordant for both intensity and volume of leisure physical activity at baseline in both 1975 and 1981 were systematically identified. Mortality and occurrence of chronic diseases (diabetes, hypertension, coronary heart disease defined according to reimbursable medication status) were followed for the period 1.1.1983 – 31.12.2006 for mortality and 1.1.1983 – 31.12.2004 for diseases. By end of follow-up, 19 inactive and 10 active co-twins had died. In the whole sample, HR of death adjusted for social class was 2.08 (95 % CI 1.06 – 4.09) for inactive vs. active co-twins, the HR being 2.67 (95 % CI 1.15 – 6.20) among DZ pairs with no mortality difference among the smaller number of discordant MZ pairs. The reimbursable medication analyses showed a tendency of higher risk for inactive vs. active co-twins. Among DZ pairs, HR of diabetes medication adjusted for social class was 2.73 (95 % CI 0.62 – 12.00) and HR of hypertension medication was 2.14 (95 % CI 0.94 – 4.89). This study **supports** the earlier findings that physical activity is associated with reduced mortality. **However** the difference was seen only in DZ pairs and therefore some residual genetic confounding effects on mortality cannot be excluded.

Keywords: morbidity, mortality, physical activity, prospective follow-up, twin studies

Abbreviations: DZ = dizygotic, MZ = monozygotic

Introduction

A sedentary lifestyle is one of the ten leading causes of death and disability in the world, and approximately two million deaths every year are estimated to be attributable to physical inactivity [1]. The protective effect of physical activity on coronary heart disease and all-cause mortality has been reported in many observational studies [2-13]. The present evidence shows an inverse curvilinear dose-response relation between physical activity and all-cause mortality [14, 15]. However, this association has only been investigated in observational studies and no randomized controlled trials are available to support the findings [14, 15]. This association could also be affected by genetic factors predisposing to sedentariness [16, 17], which also affects lifespan. A Swedish twin study by Carlsson et al. 2007 [12] found that physical activity independently protects against death. This study was able to tackle the issue of genetic influence and shared environment, but the study was conducted among healthy and already chronically diseased subjects. Therefore, as stated by Rankinen and Bouchard in the commentary [17], this study cannot be used to conclude the matter.

The underlying causes of difference in mortality between physically inactive and active subjects are mainly deaths from metabolic syndrome and cardiovascular diseases. Genetic selection and shared environmental factors may play a role towards both physical activity and mortality. For example if a person due to his/her genetic susceptibility becomes ill, gains weight or has naturally low aerobic fitness this may lead to inactivity and cause selection bias in observational studies. Various studies have shown that physical fitness and ability to achieve high levels of physical activity have genetic components [11, 18, 19]. Childhood environment has also been shown to play a modest role in adult exercise

behaviour [16]. Some evidence show that inherited biological characteristics facilitate some individuals to exercise and therefore favour them with lower morbidity and mortality [11, 20, 21]. Twin [22] and adoption [23] studies have shown that genetics may also have an important role as the underlying cause for mortality, for example Swedish and Danish twin studies have suggested that the age at death from CAD has moderate to high heritability [24-27]. Although Herskind et al. 1996 [28] estimated in a Danish twin study that the heritability of longevity is quite low; i.e. 0.2, it was found in an analysis of Nordic twin data to increase after age 60 [29]**.**

In epidemiological studies, genetic selection and childhood environment may be important confounders when studying the effect of physical activity on mortality as explained in the previous paragraph. It is difficult to conduct a randomised controlled trial of the effect of physical activity on morbidity and mortality with a long enough follow-up period. Therefore we followed twin pairs prospectively for 24 years, after initial 6-year baseline discordance in intensity and volume of leisure-time physical activity, to study the association between physical activity and all-cause mortality. A second aim was to study the chronic disease mechanisms underlying the possible mortality difference by studying differences in the occurrence of diabetes, hypertension and coronary heart disease as well as difference in cancer incidences between inactive and active co-twins. Our twin pair study design takes into account genetic predisposition (monozygotic twins) and childhood home environment (monozygotic and dizygotic twins). Monozygotic (MZ) pairs are genetically identical at the sequence level and these genetic factors are controlled for, while dizygotic (DZ) twins share **on average** half of their segregating genes. Both (DZ and MZ) pairs nearly always share the same childhood environment and therefore childhood home environment is controlled for among both types of twins.

Methods

Subjects

The Finnish Twin Cohort includes all same-sex twin pairs born in Finland before 1958 and with both co-twins alive in 1967 [30]. For this study, the initial inclusion criteria were employment (including women working at home and students) in 1981 and complete data on leisure-time physical activity required for MET index calculations gathered by postal surveys in 1975 and 1981. The subjects were between 24 to 60 years of age on January 1, 1982 (n=17,968) [11]. All pairs in which at least one of the twins did not respond to both questionnaires, had died or had a chronic disease, except hypertension, by the end of 1982 were excluded [8, 11, 30]. The healthy cohort comprised 5663 same-sex twin pairs (3551 dizygotic, 1772 monozygotic and 340 pairs with unknown zygosity) [11]. Zygosity determination was based on an accurate and validated questionnaire method [31]. Finally, included in this study were 146 same-sex twin pairs who were discordant for leisure-time physical activity in both participation in vigorous activity and volume of activity in 1975 and 1981. The mean age of the subjects was 38.1 years at the beginning of the follow-up (1.1.1983). The final study cohort (146 pairs) consisted of 65 male and 81 female pairs, of which 29 were monozygotic, 116 dizygotic and one of uncertain zygosity.

Assessment of predictors

The subjects had been mailed similar questionnaires in 1975 and 1981. These included questions on weight, height, physical activity, occupation, alcohol use, smoking and physician-diagnosed diseases. Among those for whom addresses were known (93.5 percent of subjects) in 1975, the response rate for twin pairs was 87.6 percent. The response rate among those responding in 1975 and alive in 1981 was 90.7 percent in 1981. Physical

activity habits assessed by identical questions in 1975 and 1981 were used as the baseline predictor in the present study. These data are considered to be valid on the bases of earlier studies [8, 32-35]. Our earlier analysis showed high correlations between physical activity questions and physical activity data obtained by interview [36]. In other prospective studies using the entire twin cohort, low activity metabolic equivalent (MET) index has been shown to be a predictor of mortality, type 2 diabetes, coronary heart disease and hospitalization [8, 11, 37-39].

For the current study, 146 same-sex twin pairs were comprehensively selected from the entire Finnish Twin Cohort on the basis of discordance for leisure-time physical activity both for participation in vigorous activity and volume of activity (MET index) in 1975 and 1981. Assessment of participation in vigorous physical activity in 1975 and 1981 was based on the following question: Is your leisure-time physical activity about as strenuous on average as: 1) walking, 2) alternately walking and jogging, 3) jogging (light running), 4) running. Those who chose alternatives 2, 3 or 4 were classified as participating in vigorous activity. Assessment of the MET index was based on a series of structured questions [8, 32] on leisure physical activity (monthly frequency, mean duration and mean intensity of sessions) and physical activity during the journey to and from work. The index was calculated by assigning a MET score to each activity and by calculating the product of that activity: intensity x duration x frequency [8]. The MET index was expressed as the sum-score of leisure MET hours per day. Subjects whose volume of activity was ³ 2 MET hours/day (corresponding to about 30 min walking per day) were classified as physically active compared to their inactive co-twins whose level of activity was < 2 MET hours/day. In 1975 the leisure-time MET index for 146 twin pairs was 4.59 MET hours/day for active and 0.71 MET hours/day for inactive co-twins. In 1981 the MET index was 5.80 MET

hours/day for active and 0.84 MET hours/day for inactive co-twins. **Similar MET values were seen for men, women, and MZ and DZ pairs.**

For the present study self-reported smoking status, use of alcohol, work-related physical activity at baseline in 1981 and social class in 1975 were used as covariates. Smoking status was coded into four categories (never smoked, former smoker, occasional smoker, and current (daily) smoker) determined from responses to detailed smoking history questions [34]. Alcohol use was a dichotomous index of binge drinking and defined by whether the subject had drunk at least five drinks on a single occasion, at least monthly [33]. Social class had six categories (for categories see table 1), and the classification was based on job title according to the Central Statistical Office of Finland [40]. Work-related physical activity was used as a categorical variable with four-point ordinal scale [11]. A four-question ordinal scale on life satisfaction (LS) yielded a sum score ranging between 4-20, with an increasing score indicating a decrease in life satisfaction [41]. The life satisfaction scale correlates well ($r>0.6$) with depressiveness on the Beck Depression Inventory [41].

Mortality assessment

All-cause mortality during the follow-up was analysed. The mortality follow-up began on January 1, 1983 and continued until December 31, 2006. For mortality assessment the dates of death were available from the Population Register Centre of Finland.

Assessment of reimbursed medication

To investigate the most likely causal pathways between physical activity and reduced mortality, type 2 diabetes, hypertension and coronary heart disease reimbursable medications were analysed. The reimbursable medication follow-up began on January 1, 1983 and continued until December 31, 2004. Reimbursable medication information for the 146 pairs was obtained from the Social Insurance Institution of Finland, which is the agency responsible for basic social security covering all residents of Finland [42]. The Social Insurance Institution of Finland reimburses whole or part of the cost of necessary medications to patients who have a medical certificate based on a diagnosis by a physician indicating the presence of a severe chronic disease [43]. Although the register is not sensitive to cases of a mild disease, it has very high validity and the possibility of false positive cases is unlikely [42]. The date of being granted the right to reimbursable medication was used in the analysis.

Assessment of Cancers

Information on cancers (primary site and time of diagnosis) was obtained from the population-based Finnish Cancer Registry. The cancer follow-up began on January 1, 1983 and continued until December 31, 2004. Having cancer was determined according to the first diagnoses. Cancers that physical activity is known to protect against, i.e. breast cancer and colon cancer [44, 45], were also analysed separately as one group.

Statistical Analysis

First, we conducted a mortality analysis and calculated hazard ratios (HR) with their 95 % confidence intervals (CI) for 146 physical activity discordant twin pairs using the Cox

proportional hazard model clustering for family. We then adjusted the model for social class, smoking status and alcohol use at baseline by adding one covariate at the time into the model. Similar analyses were carried out for reimbursable medications and occurrence of cancers. Follow-ups for all the endpoints were started on January 1, 1983, which allows for a lag of one year from the second physical activity assessment. The follow-up ended on December 31, 2006 or at emigration or death and for the medication analyses at the time when reimbursable medication status was granted or for cancer analysis at the time of the first cancer diagnosis or at end of follow-up (31.12.2004). All of these analyses were then carried out separately for MZ and DZ pairs. Three co-twins were excluded from all of the analyses, as they had emigrated before the follow-up start date, and 10 co-twins were excluded from the hypertension and a combination medication analyses, as these subjects had been granted hypertension reimbursable medication before the follow-up start date. Active co-twins were used as the reference group in all of the analyses. To test whether the hazard ratios differed by zygosity, a test of interaction between physical activities within discordant pairs and zygosity (MZ vs. DZ) was used. Data were analyzed with SPSS 14.0 for Windows [46] and STATA 9.0 [47] statistical packages.

Results

The baseline characteristics of the study cohort for 1975 and 1981 are shown in table 1. In both years there were more inactive co-twins who had ever smoked regularly and whose work-related physical activity was heavier when compared with active co-twins. Inactive co-twins had higher BMI in 1981 compared to their active co-twins. Inactive co-twins were less satisfied with their life in 1975, but this was not seen in 1981.

29 co-twins died during the follow-up (1.1.1983 – 31.12.2006). Mean age for all deaths was 57.1 years, inactive co-twins died on average at age of 56 and active at age of 59.3 years. All together 19 inactive and 10 active co-twins died, including 16 inactive and 7 active DZ co-twins and 3 inactive and 3 active MZ co-twins. Among the 29 individuals who died during the follow-up, both co-twins in 4 pairs died, including 2 active and 2 inactive co-twin who died before their co-twins. Figure 1 shows the survival curves for inactive and active co-twins. Inactive co-twins had increased risk of death when compared with their active co-twins (HR=1.95, 95 % CI 0.99 – 3.84). After adjusting for social class, the HR was 2.08 (95 % CI 1.06 – 4.09). When adjusted for work-related physical activity instead of social class the HR was 1.97 (95 % CI 1.01 – 3.85). Although the study had a fairly low number of subjects and a low number of outcomes, we adjusted the model for other covariates. The hazard ratios remained similar after the further adjustments (table 2). The hazard ratios increased even further when the analyses were done for DZ pairs only, the HR adjusted for social class being 2.67 (95 % CI 1.15 – 6.20). When analysing MZ pairs, no differences were seen between inactive and active co-twins. The result of the activity discordance x zygosity interaction test for mortality was not significant.

The reimbursable medication analyses showed that among the 146 pairs, 23 inactive and 20 active co-twins (19 inactive and 14 active DZ co-twins) had at least one of the studied reimbursable medications. Among the individual medication groups, 8 inactive and 6 active co-twins had medication for diabetes (8 inactive and 3 active DZ co-twins), 18 inactive and 12 active co-twins (16 inactive and 8 active DZ co-twins) had medication for hypertension, and 7 inactive and 6 active co-twins (5 inactive and 5 active DZ co-twins) had medication for coronary heart disease. The reimbursable medication analyses showed a

tendency for higher hazard ratios for inactive vs. active co-twins. Figure 2 shows the survival curves for the combined medication variable for inactive and active co-twins. Among DZ pairs, inactive co-twins had higher risk for hypertension medication during the follow-up compared to their active co-twins (HR=2.19, 95 % CI 1.00- 4.78), when adjusting for work-related physical activity HR was 2.21 (95 % CI 1.02 – 4.79). Again, no differences were seen within MZ pairs.

The cancer analyses showed that 12 inactive and 9 active co-twins (10 inactive and 7 active DZ co-twins) had at least one cancer in any site during the follow-up. The analyses showed that inactive co-twins had a slightly (but statistically non-significantly) increased risk for any cancer (table 2) compared to their active co-twins (HR adjusted for social class = 1.42, 95 % CI 0.61 – 3.33). The physical activity-related cancer analyses showed that 7 individuals, 4 inactive and 3 active co-twins, had either breast or colon cancer.

Discussion

Our over 24-year follow-up twin study assessed the relationship between physical activity and all-cause mortality. The all-cause mortality assessment showed that inactive co-twins were more likely to die earlier than their active co-twins including when childhood family environment was controlled for. Our study also investigated the possible disease mechanisms underlying the all-cause mortality difference by studying the risk of having reimbursable medication for type 2 diabetes, hypertension or coronary heart disease. The medication analyses showed a tendency for higher hazard ratios for inactive co-twins, especially for hypertension medication.

In an earlier study, we interviewed 111 pairs of twins from the original sample of 146 pairs and found that the discordant pattern of physical activity continued for a subgroup of 42 pairs for 30 years [36]. That study showed that the adulthood physical activity habits are often maintained for long time, and thus it is possible that the continuation of physical activity habits partly explains the difference in mortality. However, incipient disease from other causes can reduce the ability to exercise and thus attenuate within-pair differences in physical activity over time.

As expected, premature mortality was reduced with physical activity. This finding is in accordance with earlier studies [2-10, 12, 48]. Although a similar study **including partly** the same study population was conducted by Kujala et al. in 2002 [11], the present study concentrated on a smaller, **but** more discordant group of twins over a longer follow-up period. The main difference between the studies was more strict determination of **leisure-time physical activity** between discordant pairs taking into account both intensity and volume of leisure-time physical activity in the present study compared with the earlier study by Kujala et al. [11]. Also new cases of death had occurred since the previous study. Both analyses showed an association between high physical activity and reduced mortality in DZ twin pairs but not in MZ pairs [11], although the present study used survival analyses methods for pairwise analyses which were not used in the previous study. **Lately published Physical Activity Guidelines Advisory Committee Report,2008** [15] **shows that physical activity is clearly associated with reduced all-cause mortality, but our study indicates that there is a possible genetic pleiotropy underlying physical activity and mortality.** The present study clearly shows **and supports the extant literature** that this issue needs to be studied further, maybe among internationally pooled datasets. In the present study, we in addition examined morbidity underlying the mortality differences.

Few review studies have estimated that energy expenditure of at least 1000 kcal/week is likely to decrease mortality rates [10, 14], although both reviews acknowledged that a lesser volume of physical activity could also have beneficial effects on all-cause mortality. In our study, active co-twins exercised at least 2 MET hours/day (on average 4.59 MET hours/day in 1975 and 5.80 MET hours/day in 1981) and the intensity of activity was vigorous in two separate baseline years. This indicates that the activity level of these twins was relatively high during this 6-year period.

The mortality difference found in our study could partly be due to differences in type 2 diabetes, hypertension or coronary heart disease as a slight increase in the use of medications for these was seen among inactive co-twins. The use of hypertension medication in particular was higher among inactive co-twins. It is known that physical inactivity is a risk factor for hypertension [49, 50], and increased blood pressure is a predictor of mortality [51-53]. However, we were not able to confirm that physical activity is the major reason for this difference as we did not obtain similar results for MZ pairs, and therefore the possibility of genetic selection towards premature mortality remains. On the other hand, the number of MZ pairs was very small. The actual causes of death were available until the end of 2003. Among the 15 inactive co-twins who died by the end of 2003, the causes of death were 7 cancers, 3 cardio- or cerebrovascular diseases, 2 suicides, 1 disease of respiratory system, 1 alcohol related disease and 1 accidental fall. So, increased prevalence of T2D and CVD does not alone explain the increased mortality of physically inactive co-twins. However, a number of these causes of death are associated with physically inactive lifestyle, such as some cancers [15], CVD [2, 3, 15], pulmonary disease [54], alcohol related problems [55] and accidental falls [15].

The strengths of our study were a very long follow-up period and twin study design. We partly controlled for genetic factors and the childhood environment by studying twin pairs comprehensively selected from the large Finnish Twin Cohort. Another strength of the study was the 6-year baseline assessment period during which physical activity discordance was assessed twice, indicating a true and long-term difference in this particular health habit before the follow-up period began.

One of the limitations of the study was the low mortality rate as only 9.9% of the original sample had died; likewise the number of outcomes was small for medications and cancers. Our relatively young and healthy (exclusion of subjects with any disease but hypertension) study population at baseline contributed to this low rate of outcomes. Finally, one of the co-twins of each pair was relatively active indicating the existence of a healthy lifestyle for at least half of the subjects, while the other half were genetically closely related. **One other possible limitation relates to childhood environment as the twins might have some differences in non-shared environmental effects outside home.**

The optimal study design for this type of analysis would have been to use a large sample of activity-discordant MZ pairs. However, we did not have sufficient numbers of discordant MZ pairs, even in this large twin cohort that initially included all same-sex Finnish twin pairs who were born in Finland before 1958. So for the main analyses, the MZ pairs were pooled together with the DZ pairs. Among the baseline cohort of 5663 (31% MZ and 63% DZ) healthy twin pairs a sub-sample of 146 (20% MZ and 80% DZ) pairs were selected for the follow-up study. The reduced number of MZ pairs in our sample is probably due to the finding that MZ pairs consistently discordant for common traits are rare [8, 36, 56]. In

addition, high heritability of persistent physical activity makes it difficult to find MZ twin pairs discordant both for physical activity and mortality. The number of MZ pairs, the relatively small overall sample size and the small number of outcome events among MZ twin pairs does not make it possible to draw conclusions separately for MZ pairs. This is an unfortunate study limitation. The significant difference in the DZ pairs suggests that the association between physical activity and the outcome variables is not due to childhood environmental effects, but we cannot of course exclude the effect of genetic predisposition on the results. A Swedish twin study by Carlsson et al. 2007 [12] found a difference in mortality among activity-discordant MZ pairs, but their study had limitations as they did not exclude subjects with chronic diseases at baseline [12, 17]. Although we only had a small number of MZ pairs, the study shows that it is important to investigate the genes which are associated with both physical activity and the underlying causes of diseases.

Conclusion

This study **supports** the earlier findings that physical activity is associated with reduced mortality. **However** the difference was only seen in dizygotic pairs and therefore some residual confounding due to genetic effects on mortality cannot be excluded.

Conflict of Interest Statement

The authors have no potential conflicts of interest related to the funding.

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Figure legends

Figure 1. Survival curves for mortality for all physical activity discordant pairs and for physical activity discordant DZ pairs.

Figure 2. Survival curves for combined medication variable for all physical activity discordant pairs and for physical activity discordant DZ pairs.

Table 1. Baseline characteristics in 1975 and 1981 for 146 twin pairs.[a]

	146 pairs in 1975			146 pairs in 1981		
Characteristics	**Inactive**	**Active**	**P value**	**Inactive**	**Active**	**P value**
Age (SD)	30.1 (8.1)	30.1 (8.1)		36.1 (8.1)	36.1 (8.1)	
Height (SD)	168.5 (8.5)	169.5 (8.5)	0.027	168.8 (8.6)	169.6 (8.3)	0.065
Weight (SD)	64.6 (12.4)	64.9 (10.9)	0.73	68.1 (13.2)	66.3 (10.9)	0.036
BMI (SD)	22.6 (3.1)	22.5 (2.5)	0.59	23.8 (3.4)	23.0 (2.5)	0.003
Ever regular smoker, N (%)	83 (56.8%)	67 (45.9%)	0.037	85 (58.2%)	65 (44.5%)	0.008
Pack years smoked (SD)	4.2 (6.2)	2.6 (4.9)	<0.001	6.9 (9.8)	3.4 (6.6)	<0.001
Years smoked (SD)	9.9 (7.0)	7.7 (5.7)	0.003	15.0 (7.3)	11.5 (7.5)	0.002
Alcohol grams/day (SD)	8.1 (13.4)	9.0 (15.4)	0.49	8.4 (13.4)	7.5 (9.4)	0.46
Binge drinking, N (%)	30 (20.8%)	34 (23.6%)	0.59	36 (24.8%)	30 (20.7%)	0.39
Diagnosed hypertension, N (%)	8 (5.6%)	8 (5.6%)	1.00	15 (10.3%)	9 (6.2%)	0.26
Life satisfaction (SD) [b]	8.8 (2.7)	8.0 (2.5)	0.004	8.6 (2.6)	8.2 (2.9)	0.28
Marital status, N (%)			0.097			0.089
Single	42 (28.8%)	57 (39.0%)		28 (19.2%)	27 (18.5%)	
Married	91 (62.3%)	83 (56.8%)		102 (69.9%)	99 (67.8%)	
Divorced	6 (4.1%)	4 (2.7%)		6 (4.1%)	1 (0.7%)	
Cohabiting	5 (3.4%)	2 (1.4%)		9 (6.2%)	17 (11.6%)	
Widowed	2 (1.4%)	0		1 (0.7%)	2 (1.4%)	
Work-related physical activity, N (%)			0.019			0.012
Sedentary	47 (32.4%)	57 (39.3%)		48 (33.3%)	64 (44.4%)	
Standing or walking at work	26 (17.9%)	32 (22.1%)		23 (16.0%)	30 (20.8%)	
Light manual labour	61 (42.1%)	52 (35.9%)		51 (35.4%)	43 (29.9%)	
Heavy manual labour	11 (7.6%)	4 (2.8%)		22 (15.3%)	7 (4.9%)	

Social class, N (%)		
Upper white-collar worker	11 (7.5%)	13 (8,9%)
Clerical worker	48 (32.9%)	51 (34.9%)
Skilled worker	48 (32.9%)	52 (35.6%)
Unskilled worker	11 (7.5%)	11 (7.5%)
Farmer	19 (13.0%)	3 (2.1%)
Other (Students, army, retired, unknown)	9 (6.2%)	16 (11.0%)

[a] Plus-minus values are means ±SD.

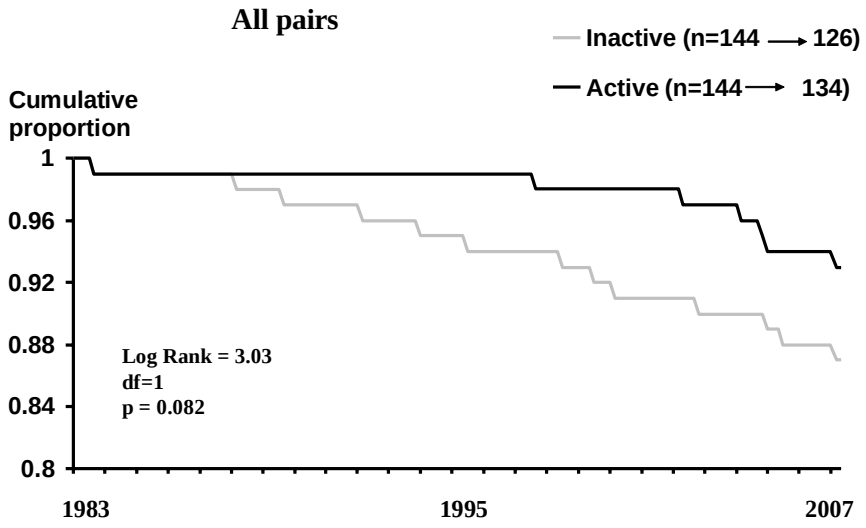
[b] The life satisfaction index was a four-question scale with sum score ranging from 4-20, with an increasing score indicating a decrease in life satisfaction.

Table 2. Hazard ratios for death, cancers and reimbursable drug use for inactive co-twins compared with active co-twins, adjusted for variables in 1975 (social class) or variables in 1981 (alcohol and smoking).

	Discordant			**Social class adj.**			**Social class, alcohol and smoking adj.**		
All pairs	**HR**	**95 % CI**	**p**	**HR**	**95 % CI**	**p**	**HR**	**95 % CI**	**p**
Mortality	1.95	0.99 - 3.84	0.054	2.08	1.06 – 4.10	0.034	2.04	0.94 – 4.42	0.072
Diabetes [a]	1.39	0.47 - 4.13	0.55	1.25	0.40 – 3.88	0.70	1.22	0.40 – 3.74	0.73
Hypertension [a]	1.57	0.78 - 3.13	0.21	1.50	0.73 – 3.08	0.27	1.71	0.82 – 3.57	0.16
CHD [a]	1.21	0.54 - 2.72	0.65	1.08	0.40 – 2.91	0.89	0.96	0.21 – 4.43	0.96
All med. [b]	1.20	0.73 - 1.96	0.47	1.14	0.67 – 1.92	0.63	1.27	0.71 – 2.26	0.43
Cancers [c]	1.37	0.61 - 3.06	0.45	1.42	0.61 – 3.33	0.42	1.34	0.49 – 3.65	0.57
DZ pairs	**HR**	**95 % CI**	**p**	**HR**	**95 % CI**	**p**	**HR**	**95 % CI**	**P**
Mortality	2.41	1.05 - 5.54	0.039	2.67	1.15 – 6.20	0.022	2.61	1.08 – 6.29	0.033
Diabetes [a]	2.91	0.74 - 11.4	0.13	2.73	0.62 – 12.00	0.18	2.61	0.58 – 11.73	0.21
Hypertension [a]	2.19	1.00- 4.78	0.049	2.14	0.94 – 4.89	0.072	1.97	0.80 – 4.87	0.14
CHD [a]	1.08	0.41 - 2.86	0.88	0.84	0.21 – 3.40	0.80	1.06	0.34 – 3.28	0.93
All med. [b]	1.49	0.85 - 2.62	0.17	1.39	0.73 – 2.65	0.32	1.46	0.72 – 2.96	0.30
Cancers [c]	1.50	0.63 - 3.60	0.36	1.52	0.60 – 3.85	0.38	1.56	0.54 – 4.53	0.41
MZ pairs	**HR**	**95 % CI**	**p**						
Mortality	0.96	0.35 - 2.60	0.93						
Hypertension [a]	0.44	0.08 - 2.57	0.36						
All med. [b]	0.59	0.21 - 1.68	0.33						
Cancers [c]	0.97	0.13 - 7.32	0.98						

CI denotes confidence interval. [a] Reimbursable medication. [b] All medications includes diabetes, hypertension and CHD reimbursable medications. [c] Any cancer.

Figure 1.


All pairs
Inactive (n=144 → 126)
Active (n=144 → 134)
Cumulative proportion
1
0.96
0.92
0.88
0.84
0.8
Log Rank = 3.03
df=1
p = 0.082
1983
1995
2007

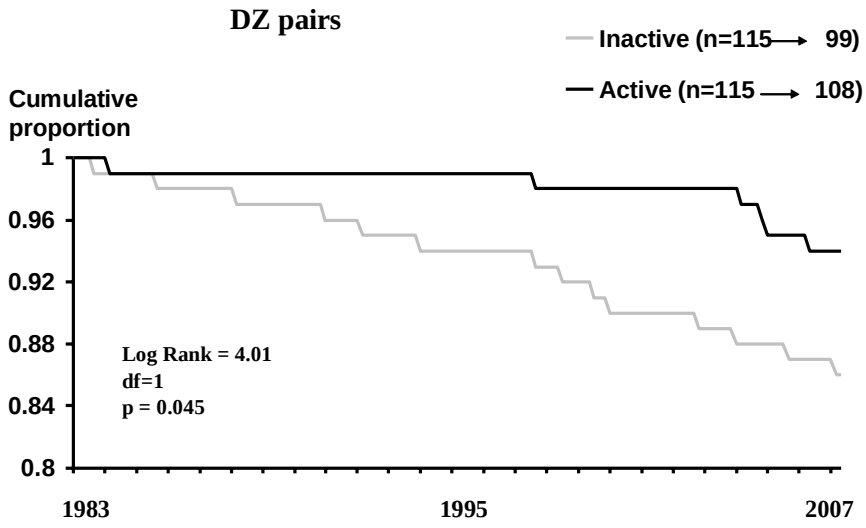
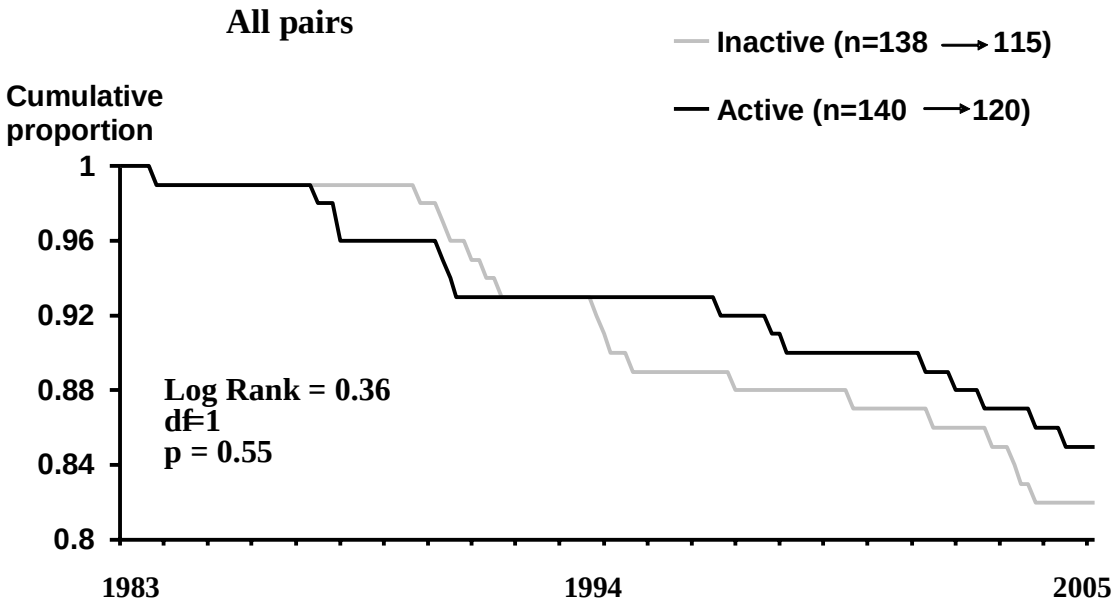
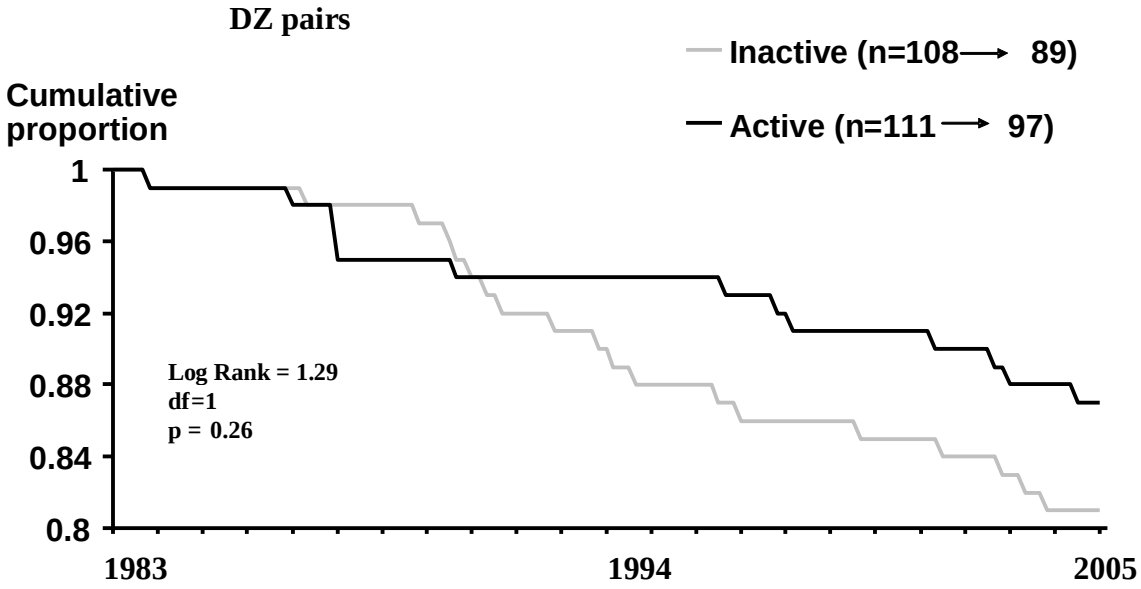

DZ pairs
Inactive (n=115 → 99)
Active (n=115 → 108)
Cumulative proportion
1
0.96
0.92
0.88
0.84
0.8
Log Rank = 4.01
df=1
p = 0.045
1983
1995
2007

Figure 2.


All pairs
Inactive (n=138 → 115)
Active (n=140 → 120)
Cumulative proportion
1
0.96
0.92
0.88
0.84
0.8
Log Rank = 0.36
df=1
p = 0.55
1983
1994
2005


DZ pairs
Inactive (n=108 → 89)
Active (n=111 → 97)
Cumulative proportion
1
0.96
0.92
0.88
0.84
0.8
Log Rank = 1.29
df=1
p = 0.26
1983
1994
2005