

Genetic Susceptibility to Sickness Absence is Similar Among Women and Men: Findings From a Swedish Twin Cohort

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Previous studies of risk factors for sickness absence (SA) focus primarily on psychosocial and work environmental exposures. The aim of this study was to investigate the relative contribution of genetic influences on SA among women and men. The population-based study sample of Swedish twins (34,547) included 13,743 twin pairs of known zygosity, 3,495 monozygotic, 5,073 same-sexed dizygotic, and 5,175 opposite sexed. The point prevalence of long-term SA (≥ 15 days) in each zygosity and sex group was calculated. The risk of SA was estimated as an odds ratio (OR) with 95% confidence intervals (CI) where the odds for twins on SA to have a co-twin on SA was compared to the OR for SA in twins whose co-twin were not sickness absent. Intrapair correlations and probandwise concordance rates were calculated and standard biometrical genetic model-fitting methods were used to estimate the heritability of SA. The prevalence of SA was 8.8% (women 10.7%; men 6.5%). Intrapair similarity was higher among monozygotic than dizygotic twin pairs. The best-fitting model showed no sex differences in genetic effects or variance components contributing to SA. The heritability estimate was 36% (95% CI: 35–40%). Results suggest genetic contribution to the variation of SA and that environmental factors have an important role, for women and men. As SA seem to be influenced by genetic factors, future studies of associations between risk factors and SA should consider this potentially confounding effect.

■ **Keywords:** sick leave, sickness absence, heritability, twins, register, Sweden, genetic, environmental

Several studies have investigated risk factors for sickness absence (SA) as well as factors predicting the duration of a sick leave spell (Alexanderson & Norlund, 2004a, 2004b; Dekkers-Sanchez et al., 2008; Steenstra et al., 2005). Focus has been on different types of psychosocial and work environmental factors, and the variation in those were suggested to be affected by selection, for instance selection into certain types of jobs, social context, or lifestyle (Alexanderson & Norlund, 2004a, 2004b; Allebeck & Mastekaasa, 2004). Even though some studies have included information on the diagnosis underlying the work incapacity, mostly biological factors including genetic, have not been studied, mainly due to lack of such data. Nevertheless, influence of genetic factors may affect the estimations of the influential factors on SA if present, since genetic factors may be unknown confounders in studies of associations between risk factors and SA (Alexanderson & Norlund, 2004a, 2004b; Allebeck & Mastekaasa, 2004; Pietikäinen et al., 2011; Ropponen et al., 2011a, 2011b; Samuelsson et al., 2012).

Studies of twins would provide additional insight into these issues.

One prerequisite for sickness benefits is the presence of a disease or injury, the other prerequisite is that this disease or injury has led to work incapacity. The pathways leading to SA might include biological factors affected by the presence of a disease or health symptoms, but also factors related to the work situation, insurance system, family background, socio-economy, demography, lifestyle, and culture can influence the SA of a person (Alexanderson & Norlund, 2004b; Allebeck & Mastekaasa, 2004; Pietikäinen et al., 2011; Ropponen et al., 2011a, 2011b; Samuelsson et al., 2012).

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Thus, familial (genetic and family/early environment) as well as environmental factors may have important roles in individual differences in SA. So far, no twin or family study has investigated the relative contribution of genetic and environmental factors to SA. However, two recent studies have investigated genetic liability to disability pension (DP) (Harkonmaki et al., 2008; Narusyte et al., 2011). DP is defined as an ultimate consequence of permanent work incapacity due to medical causes, and genetic factors were shown to contribute to the liability to DP to a moderate degree (24–49%), somewhat varying depending on DP diagnose group (Harkonmaki et al., 2008; Narusyte et al., 2011). Diagnoses behind SA are to a large extent the same as those behind DP, that is, mental and musculoskeletal diagnoses (Hansson & Jensen, 2004; Järvisalo et al., 2005). However, there might also be a variety of other SA diagnoses that cause work incapacity for a shorter time period that does not necessarily lead to permanent work incapacity and subsequent DP.

The present study aims to investigate the relative contribution of genetic and environmental factors for being SA among women and men in a large population-based Swedish twin cohort. A comparison of SA in monozygotic (MZ) and dizygotic (DZ) twin pairs would provide new insights on whether genetic factors influence SA. Inclusion of both women and men and opposite-sexed (OS) twins also enables further investigation of sex differences in the relative importance of genetic factors as well as whether different genes operate in women than in men. We expect that MZ twins are more similar than DZ twins for SA, based on previous findings of such similarities regarding DP and in occurrence of common diseases (Harkonmaki et al., 2008; Narusyte et al., 2011; Plomin et al., 1994, 2000).

Methods

Participants and Data Sources

This study is based on the Swedish Twin study Of Disability pension and Sickness absence (STODS), established in 2009 (Svedberg et al., 2010). STODS includes twins born in Sweden between 1925 and 1958 (29,799 twin pairs) who were identified through the Swedish Twin Registry (STR) (Lichtenstein et al., 2002). Individuals who were on DP, old-age pension, or who were 65 years or older at January 1, 2002 were excluded. Hence, the study sample ($n = 34,547$) included twins born 1938–1958 (49.4% women) whereof 13,743 twin pairs of known zygosity; 3,495 MZ, 5,073 same-sexed DZ, and 5,175 OS DZ pairs.

All people living in Sweden with income from work or unemployment benefits are covered by the public Social Insurance, providing sickness benefits when disease or injury has led to work incapacity, covering about 80% of lost income. SA data were retrieved from the Swedish National Social Insurance Agency's MiDAS database. For employees, sick pay is provided by the employer for the first 14 days of a

SA spell, and thus not included in the MiDAS database. Data on death was obtained from the National Board of Health and Welfare, and data on old-age pension were obtained from Statistics Sweden. All registry data was linked to the twins by using the unique 10-digit personal identification number assigned to all Swedish residents.

Measures

Being long-term SA was defined as a binary variable (yes/no) based on the data in the MiDAS database at the National Social Insurance Agency at January 1, 2002, that is, having an ongoing sick leave spell of a duration of at least 15 days at this date.

In order to establish the *zygosity* of the like-sexed twin pairs, a series of questions about similarity was asked at the time of STR compilation. If twins in a pair did not agree on similarity, these questions were repeated in a later interview. The zygosity diagnosis was confirmed using DNA markers in a subset of the sample, and proved correct in 98% of the pairs (Lichtenstein et al., 2002, 2006).

Design and Statistical Analysis

Cross-sectional data analyses were conducted. The point prevalence of SA in each zygosity and sex group was calculated as the number of individuals on SA compared to all individuals in the group. The risk of SA was estimated as an odds ratio (OR) with 95% confidence intervals (CI) where the odds for twins on SA to have a co-twin on SA was compared to the odds for SA in twins whose co-twin was not sickness absent. Twin similarity in a pair was measured by calculating intrapair tetrachoric correlations as well as probandwise concordance rates. These rates refer to the conditional probability that one twin is affected, given that his or her co-twin is affected, which is compared with the probability of SA for an individual in the general population. SAS statistical software was used for these analyses (SAS Institute Inc, 2003).

Standard biometrical genetic model-fitting methods were used to investigate the heritability of SA, i.e., the proportion of variance accounted for by genetic factors. Genetic models were fitted to the raw ordinal data by maximum likelihood using Mx (Neale et al., 2006). Analyses focused on fitting models allowing for additive (A) genetic effects plus shared (C) and nonshared (E) environmental effects. The goodness-of-fit of the full ACE model (i.e., the model including all A, C, and E effects) was compared to that of the restricted models (AE, CE, and E) by likelihood ratio tests. Akaike's information criterion (AIC) is an index of both goodness-of-fit and parsimony, which was also calculated for each fitted model. The model with the lowest AIC value was chosen as the best-fitting model, explaining the data in the most parsimonious way. Inclusion of opposite-sex twins provides an opportunity to test whether different genes are operating in women than in men (Kendler et al., 1992; Neale et al., 2006). If contributing genetic effects are not the same

TABLE 1

Number of Concordant Twin Pairs, Probandwise Concordance Rates, Odds Ratios (OR) with 95% Confidence Intervals (CI), and Tetrachoric (Intraclass) Correlations of Sickness Absence (SA) in a Swedish Twin Cohort for Monozygotic (MZ), Dizygotic (DZ) Same-Sexed, and DZ Opposite-Sexed (OS) Pairs

Participants	Concordant pairs SA (n)	Discordant pairs (n)	Concordant pairs not SA (n)	Probandwise concordance rate ^a	Tetrachoric correlation (95% CI)	OR (95% CI) ^b
All						
MZ	55	385	3,055	22%	0.40 (0.33–0.46)	4.55 (3.36–6.35)
DZ	52	672	4,349	13%	0.18 (0.12–0.24)	2.00 (1.47–2.75)
OS	41	762	4,367	11%	0.08 (0.02–0.14)	1.40 (1.01–1.93)
Men						
MZ	12	146	1,539	14%	0.30 (0.18–0.41)	3.47 (1.80–6.67)
DZ	12	259	2,360	8%	0.12 (0.01–0.22)	1.69 (0.91–3.14)
Women						
MZ	43	239	1,516	26%	0.42 (0.34–0.50)	4.61 (3.11–6.86)
DZ	40	413	1,989	16%	0.17 (0.10–0.25)	1.87 (1.29–2.70)

Note: ^aAn individual's risk of SA (the conditional probability that one twin is affected, given that his or her co-twin is affected) and as such can be compared with the probability of SA for an individual in the general population. ^bThe risk of SA was calculated as an odds ratio where the odds for individuals on SA having a twin partner on SA was compared to the odds for SA in a twin whose co-twin were not sickness absent.

between the two sexes, the estimated genetic correlation (r_g) for the opposite-sex twins should be significantly different from a genetic correlation between the same-sex DZ twins, that is, 0.5. For estimation of all variance components as well as r_g , we used all zygosity and sex groups simultaneously (MZ male, DZ male, MZ female, DZ female, DZ OS male–female, DZ OS female–male). We started out by fitting a model with all parameters being freely estimated, that is, ACE and prevalence parameters were different for women and men, as well as freely estimated r_g (Model 1). Thereafter, the following restricted models were tested: Model 2 included free ACE parameters, but the same prevalence parameters for men and women, and freely estimated r_g . Model 3 included free ACE parameters, but different prevalence parameters for men and women, and r_g fixed at 0.5. Model 4 constrained ACE parameters to be equal across sex and r_g fixed at 0.5, but different prevalence for men and women. Models 5 and 6 were the submodels AE and CE, respectively.

The study was reviewed and approved by the Regional Ethical Committee in Stockholm, Sweden.

Results

Among all individuals in the study sample (34,547), 2,964 twins were identified as having a long-term SA spell (8.6%) at January 1, 2002. SA was more prevalent among women (10.7%) than men (6.5%). The probandwise concordance rates were higher among MZ than DZ twin pairs and the tetrachoric intrapair correlations for each zygosity and sex group are presented in Table 1. The correlations in the MZ twin pairs were higher than the within pair correlations for DZ twin pairs in both sexes, suggesting a significant contribution of genetic factors in SA. The correlations for MZ female twin pairs were somewhat higher than the MZ male correlations suggesting sex differences in heritability. Further, the correlation in DZ OS twin pairs was lower (0.08) than the correlations for DZ same-sexed twin pairs

TABLE 2

Model Fit Statistics For the Univariate Model of Genetic and Environmental Effects in Liability to Sickness Absence in a Swedish Twin Cohort

Model	Fit of model					
	-2LL	df	Δ df	$\Delta\chi^2$	p-Value	AIC
1	18,717.84	32,673				
2	18,915.51	32,674	1	197.67	0.00	195.67
3	18,718.52	32,674	1	0.68	0.41	-1.32
4	18,722.65	32,677	4	4.81	0.31	-3.19
5 ^a	18,722.65	32,678	5	4.81	0.44	-5.19
6	18,740.89	32,678	5	23.05	0.00	13.05
7	18,771.27	32,679	6	79.73	0.00	67.73

Note: LL = log-likelihood; df = degrees of freedom. ^aBest-fitting and the most parsimonious submodel (AE allowing different thresholds for women and men) indicated by the lowest Akaike's information criteria (AIC) value. Model 1 (full model): ACE women \neq ACE men, different threshold for males and females, r_g estimated. Model 2: ACE women \neq ACE men, same threshold for males and females, r_g estimated. Model 3: ACE women \neq ACE men, different threshold for males and females, r_g fixed. Model 4: ACE women = ACE men, different threshold for males and females, r_g fixed. Model 5: AE women = AE men, different threshold for males and females, r_g fixed. Model 6: CE women = CE men, different threshold for males and females. Model 7: E women = E men, different threshold for males and females.

($r = 0.17$ for women, $r = 0.12$ for men), suggesting sex differences in genetic effects for SA.

All the ORs were statistically significant for all zygosity groups by sex except for same-sexed DZ male twins. ORs were higher for MZ than DZ twins with MZ women showing the highest risk (OR = 4.61, CI = 3.11–6.86) (Table 1).

Before conducting the biometrical genetic analyses, a saturated model was used to test assumptions of twin models, and it was possible to constrain the thresholds for SA to be equal in twin 1 and twin 2 in a pair, in MZ and DZ same-sex pairs, and in same-sex and opposite-sex pairs.

The model fitting started with a full model (Model 1 in Tables 2 and 3). In Model 1, additive genetic effects (A), shared environmental effects (C) and nonshared environmental effects (E) were allowed to vary across sexes, different prevalence levels were allowed for men and women (two

TABLE 3

Parameter Estimates of Genetic and Environmental Effects with 95% Confidence Intervals (CI) in Liability for Sickness Absence in a Swedish Twin Cohort from Univariate Model-Fitting, Full Model, and Most Parsimonious (Best-Fitting) Model

Model	Parameter estimate						
	Men			Women			
	a^2	c^2	e^2	a^2	c^2	e^2	r_g
Full ACE model ^a	0.32 (0.28–0.46)	0.00 (0–0.27)	0.68 (0.54–0.85)	0.43 (0.20–0.52)	0.00 (0–0.17)	0.57 (0.48–0.68)	0.29
Best-fitting model ^b	0.36 (0.31–0.40)		0.64 (0.57–0.72)	0.36 (0.31–0.40)		0.64 (0.57–0.72)	0.50

Note: ^aFull model: ACE women \neq ACE men, different thresholds for males and females, r_g estimated. ^bBest-fitting and the most parsimonious submodel (AE women = AE men, allowing different thresholds for women and men), and r_g fixed, as indicated by the lowest Akaike's information criteria (AIC) value.

thresholds), and the genetic correlation for OS twins (r_g) was estimated. Second, we tested for the same prevalence in men and women (Model 2), which resulted in deterioration of fit. Therefore, the subsequent models used different thresholds for men and women.

We fixed the genetic correlation for the opposite-sex twins to be equal to that of same-sexed DZ pairs (Model 3, $r_g = 0.5$) and no significant deterioration of fit was observed. Model 4 constrained ACE to be equal for men and women. Again, there was no deterioration in fit, thus providing no evidence for gender-specific effects. Working from Model 4, we compared the equal ACE model to an AE model (Model 5). The latter model was preferred to the ACE model by the AIC criterion because of greater parsimony. The CE model (Model 6) was then fitted resulting in a poorer fit than the AE model according to AIC. The model which assumes no resemblance for SA (E) fitted poorly and was also rejected. Fit statistics and model-fitting results are presented in Tables 2 and 3.

The most parsimonious and best-fitting model according to AIC was the AE model (Model 5) with no shared environment (C), equal estimates for men and women, and r_g fixed to 0.5. The results of the model fitting for this model and for the full model are provided in Table 3. In the best-fitting model, heritability was estimated at 35.6% (95% CI: 31.3–39.6%), with no sex differences in neither genetic effects nor the other variance components contributing to SA. However, prevalence of SA differed between sexes.

Discussion

This study investigated genetic liability to SA in a Swedish twin cohort of 35,000 adults aged 43–65 years. We found no support for sex differences in genetic factors contributing to SA even though prevalence of SA differed between women and men, i.e., more women than men were on SA.

To the best of our knowledge, no twin study has so far investigated the relative contribution of genetic and environmental factors to SA. The heritability of SA was 36% and of equal importance for women and men in the present study, similar to estimates recently shown for DP (Harkonmaki et al., 2008; Narusyte et al., 2011). Genetic factors may reflect genetic liability to disease, such as cardiovascular

disease (Evans et al., 2003; Zdravkovic et al., 2007), depression (Kendler et al., 2006; Orstavik et al., 2007), diabetes (Hyttinen et al., 2003), musculoskeletal disorders (Battie et al., 2007; MacGregor et al., 2004), or functional ability (Christensen et al., 2000). As diagnoses behind SA to a large extent are the same as those behind DP, which are, mental and musculoskeletal diagnoses (Hansson & Jensen, 2004; Järvisalo et al., 2005), this result could be expected. However, contrary to our expectations, the heritability of SA was not lower than that of DP. A greater variety of diagnoses, also co-occurring, might be expected behind SA that cause work incapacity for a shorter time period and hence does not necessarily lead to permanent work incapacity. Most SA spells do not lead to DP. Conditions that initially cause SA either resolve through a natural course or can to a large extent be dealt with thorough medication or other treatments, also true for many chronic conditions, such as diabetes or cardiovascular diseases (Evans et al., 2003; Hyttinen et al., 2003). Other common medical diagnoses behind SA that seldom cause permanent exclusion from the working life include influenza, pneumonia, gastrointestinal diseases, recurrent headache or migraine, asthma, chronic widespread pain, and chronic fatigue, some being more heritable conditions than others (Burgner & Levin, 2003; Ekbom et al., 2006; Kato et al., 2009; Svedberg et al., 2008; Svensson, 2004). Hence, one could also have expected that the broader variety of medical reasons behind SA than DP could have resulted in a lower heritability estimate for SA than reported for DP.

We also expected that twins in a pair would less likely be on SA at the same time as compared to for example twin similarity in DP. This expectation was based on our use of ongoing SA spells (≥ 15 days) at a specific date that were then considered as a binary measure of SA. However, as this prevalence measure included SA starting and ongoing at that time point despite of the length, recurrence, or diagnosis of SA, it might have increased the pairwise concordances. Also, this SA measure based on register data can be considered as long-term SA. Furthermore, among those on SA with one diagnosis, there is often a wide variance in future SA diagnoses whereof some might lead to permanent incapacity to work and DP (Hagberg et al., 2010; Vaez et al., 2007, 2009).

Environmental factors also had an important role in individual differences in SA and may be related to adulthood choices or other factors unique to each individual. Several studies have, for example, shown that work environmental factors, mainly physical but also psychosocial factors (Burr et al., 2011; Christensen et al., 2005; Labriola et al., 2006; Lund et al., 2006; Nielsen et al., 2006; Voss et al., 2004), lifestyle (Laaksonen et al., 2009; Robroek et al., 2011), and pain (Saastamoinen et al., 2009) are associated with SA. Further, some recent twin studies of the associations between socio-demography, health-related factors, pain, and DP showed that the associations seem to be independent from familial effects or influenced by those to a minor degree (Pietikäinen et al., 2011; Ropponen et al., 2011a, 2011b; Samuelsson et al., 2012).

In contrast to previous results of genetic liability to DP (Narusyte et al., 2011), we found no support of different pathways to SA for women and men. However, further large studies including specific diagnoses are necessary to investigate the complexity of sex and diagnose-specific effects of both SA and DP more precisely. In line with previous studies of genetic liability to DP we found no effects of shared environment (Harkonmaki et al., 2008; Narusyte et al., 2011). This finding does not necessarily imply that such factors are unimportant, only that they are not important for individual differences in SA.

Strengths and Limitations

This was a large population-based study including both same-sexed and opposite-sex twin pairs. Ascertainment bias that sometimes is a problem in twin studies was unlikely to occur since the register data of SA were of high quality and covers all individuals over the age of 16 in the Swedish population that were granted SA benefits. Further, occurrence of SA in the twin cohort was comparable to the official statistics of the Swedish National Social Insurance Agency (Försäkringskassan (Swedish Social Insurance Agency), 2011). A limitation in this study was that information on SA diagnoses was not available. Having in mind results from previous studies of DP (Harkonmaki et al., 2008; Narusyte et al., 2011), it is possible that the heritability estimates would differ depending on the medical diagnosis behind SA. Also, as younger adults below age 40 were not included in the present study, the results cannot be generalized to young adults. Further, information on short-term SA spells were not available, i.e., the relative importance of genetic and environmental factors for the very short SA might differ from our findings.

Conclusions

Both genetic and environmental factors seem to have important roles for individual differences in SA, contributing in a similar way in women and men. The relatively large proportion of the variance in SA explained by environmental factors emphasizes the importance to continue to identify

and address specific environmental stressors when planning intervention strategies for people at risk for SA. However, and more importantly, as SA seem to be influenced by genetic factors, future studies of associations between risk factors and SA should consider this potentially confounding effect.

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