Thoughts of self-harm and suicidal behavior are thought to be influenced by both genetics and environment. Molecular genetic studies are beginning to address the question of which genes may be involved and whether different genes may be expressed in men and women. We examined thoughts of self-harm and suicidal behavior in a large general population twin sample including male and female same- and opposite-sex twins. In this study, data on self-reported thoughts of self-harm and suicide were obtained from self-report questionnaires (Beck Depression Inventory and Youth or Adult Self Report forms) in 6,265 twin pairs (11,008 individuals) aged 11–90 (62% female) from the Netherlands Twin Registry. Liability threshold models were compared including sex and age (linear and quadratic) effects. Models were compared using measures of parsimony to calculate the simplest model to the data. A model with additive genetic and unique environmental contributions fitted the data for both males and females. There were no qualitative sex differences, but the relative contributions differed between men and women. Heritability was higher in women (0.74, 95% CI 0.65–0.81) than men (0.45, 95% CI 0.28–0.61). The remaining variance was accounted for by environmental influence unique to an individual. These results suggest contributions from additive genetic factors to self-reported thoughts of self-harm and suicide and support the continued study of both molecular genetic and individual-specific environmental risk factors.

Keywords: suicide; twins; behavioral genetics

Introduction
Suicidal and self-harming behavior is a complex phenomenon with multiple contributing factors, including familiality. The familial nature of suicide has been of considerable interest because the risk of suicide increases when a first-degree relative has committed suicide [Glowinski et al., 2001] and other self-harming behaviors also run in families [Distel et al., 2011]. Familial problems are not exclusively due to genetic factors and therefore it is crucial to study how much of this familiality is genetic. To date, there are many discrepancies in the literature [Arango et al., 2003; Courtet et al., 2005; Coventry et al., 2010], but indicate that the genetic basis for thoughts of self-harm and suicide is complex rather than simple [Arango et al., 2003; Wasserman et al., 2007] and worthy of further investigation [Fu et al., 2002; Arango et al., 2003; Courtet et al., 2005; Wasserman et al., 2007]. Research on the co-occurrence of other traits, for instance, has tested the relations between major depressive disorder, cluster B traits and impulsive aggressive behavior with completed suicide. Overlapping but distinct heritability for depression and suicide was found, with evidence that cluster B traits serve as intermediate phenotypes of suicide [McGirr et al., 2009].

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Behavioral and molecular genetic studies have demonstrated the heritability of self-reported thoughts of self-harm and suicide behavior (SHSB) alongside other heritable psychiatric and substance abuse phenotypes [Dick et al., 2010]. An association has been observed between perceived loneliness and attempted suicide, independent of major depression [Witkorsson et al., 2010] and early onset nicotine dependence has underlying common causes with SHSB [Kessler et al., 2009]. Presence or absence of alcohol use can interact with genes of risk specific for suicide, as demonstrated with TPH2 in Polish populations [Fudalej et al., 2009] and elevated TPH2 expression in the ventral prefrontal cortex is a characteristic of suicide completers [Perroud et al., 2010]. Other molecular genetic studies have demonstrated findings consistent with the etiopathologic pathways suggested from the neurobiological studies of suicide, as previously reviewed [Ernst et al., 2009]. Genes such as 5-HTTLPR, CRHR1, and mu-opioid-type receptors or the ROR1, CD44, FOXN3, DXH15 were identified in gene expression or GWAS studies of suicides [Wasserman et al., 2010]. In Schizophrenia patients, the HPA-axis gene CRHBP confers risk for suicide attempt, and interacts with another HPA-axis gene CRHR1 with apparent consequences for suicide attempt risk and nature of attempt [De Luca et al., 2010]. Perlis et al. [2010] recently investigated lifetime history of suicide attempt in 8,737 subjects with either bipolar disorder or major depression. SNPs associated with suicide were near the genes: TBL1XR1, IRX2, CAPN13, ZNF406, and FLJ42117, ABI3BP, SLC4A4, LRRC44, HAS1, and ARL6IP2, depending on whether the depressed or bipolar sample was examined. No such associations were found, however, in replication samples for either the bipolar or depressed subjects and they could not confirm any of 19 genetic associations with suicide attempt made by other studies including CRHBP [De Luca et al., 2010], and CRHR1 [De Luca et al., 2010; Perlis et al., 2010; Wasserman et al., 2010].

Specific to suicide, genetic differences by sex have been reported. The 5-HTTR6 gene 268 C/T SNP is reported to have a role in men but not in women in a Portuguese sample [Azenha et al., 2009]. Recent findings confirm the likelihood of sex differences in suicide risk [Cui et al., 2010; Schenkel et al., 2010]. Patients with depression had significantly more lethal suicide attempts in males, and in individuals with the BDNF 66Met allele [Schenkel et al., 2010]. A study of Japanese male and female suicide victims found that male suicide completers had a lower frequency of the minor allele of a single SNP in the NOS1 gene compared to both controls and female suicide completers [Cui et al., 2010].

The role of environment has also been noted in previous studies of both suicide and self-harm. The role of environmental risk factors such as demographic factors (including age and marital status) has been reported, interacting with stressful life events and social support [Casey et al., 2006] to influence both self-harm and suicidal thoughts. Tight-knit families appear to play a protective role [Pena et al., 2011], while children from families in which sexual or physical abuse, neglect, parental loss, or severe family discord are present are at increased risk for self-harm and suicidal thoughts [Brodsky and Stanley, 2008; Mann and Currier, 2010]. However, it is possible that some of these risk factors are themselves influenced by genotype.

Taken together these data support the idea that SHSB are influenced by genes and environmental factors, but exactly which the nature and relative magnitude of these genetic and environmental factors remains to be identified.

Twin studies have been used to address some of these questions. In a small study of monozygotic and dizygotic twins who were survivors of their co-twin’s suicide, Segal [2009] demonstrated that MZ co-twin survivors were more likely to attempt suicide than DZ survivors, suggesting a genetic component to completed SHSB. In a twin study of SHSB in 3,416 adolescent female twins, Gloswinski et al. [2001] found that for both MZ and DZ twin pairs, the presence of a co-twin with a suicide attempt was a risk factor for suicide attempt, but that the concordance rate for suicide attempt was higher in MZ than in DZ twin pairs, indicating that genetic factors may contribute to liability [Gloswinski et al., 2001]. Under the best-fitting model, estimates for additive genetic effects were 48% and for shared environmental effects 8%, although the confidence intervals around these estimates were wide (reflecting the low base rates of suicide attempts) so neither the genetic nor the shared environmental effect was statistically significant from zero.

In a twin study including 4,962 MZ and 6,046 DZ twins of both sexes, Cho et al. [2006] identified a higher, though not statistically significant concordance rate of SHSB in MZ versus DZ twin pairs. They also compared female and male twin pairs and found evidence to support the hypothesis that gender specific genetic factors may impact factors that influence thoughts of self-harm and suicide including aggression, depression, quantity of cigarettes smoked, alcohol use, and binge drinking. In a sample of 3,372 male twins from the Vietnam Era Twin Registry, Fu et al. [2002] specifically examined suicidal ideation and found that risk for both suicidal ideation and suicide attempt were influenced by shared genetic factors. In their study of 5,995 Australian twins, Statham et al. [1998] found a heritability of 44% for suicidal behavior, which was unchanged when controlling for other psychiatric symptoms. In a study of 38,469 twin pairs from the Swedish Twin Registry the concordance rate for lethal suicide in female MZ twins was 11% higher than the rate for female DZ twins, whereas the rate for male MZ twins was only 1% higher than that of male DZ twins [Pedersen and Fiske, 2010]. These findings indicate the potential for a stronger genetic contribution to lethal suicide in females versus males.

In their review of twin studies on suicide, Voracek and Loibl [2007] lament several residual problems with twin research on suicide: (1) questions of zygosity, (2) recruiting biases and reporting effects, (3) no correction for age effects in the studies, and (4) lack of systematic study of sex differences [Voracek and Loibl, 2007]. A further complication of work on suicidal thoughts and behavior is that phenotypic definitions of what comprises suicidal thoughts versus non-suicidal self-injurious behavior have impeded an undertaking of large twin studies.

The present work presents data from a population-based survey of 11,008 adolescent and adult twins from 6,265 families (4,743 complete twin pairs) with zygosity not only based on a standardized questionnaire method but also validated by DNA tests. Questions about self-reported thoughts of SHSB were answered by informants at multiple time points and using one of the most commonly used instruments for the measurement of adolescent behavior (the adolescent and young adult self-report
version of the Child Behavior Checklist) and one of the most commonly used instruments for measuring depression (the Beck Depression Inventory). Issues of phenotypic definition have been a major issue in suicide research with measures of suicidality and parasuicidality often confounded. This is also the case here. These measures are not ideal for measuring lethal suicidality specifically. Rather, the work reported here allows us to approximate general estimates of SHSB in a large sample, but with continued phenotypic confounds.

We used information on the CBCL and BDI to analyze individual differences in liability to SHSB using a liability threshold model. Age effects (linear and quadratic) were modeled on the threshold. Sex differences were both allowed on the thresholds (i.e., allowing for differences in prevalence between the sexes) and on the genetic architecture. Because same-sex male and female twin pairs and opposite-sex pairs participated in the study, it was possible to study quantitative genetic differences (including a different genetic architecture for males versus females resulting in different heritabilities) and qualitative sexual differences (i.e., whether the same genes are expressed in males and females).

MATERIALS AND METHODS

Subjects and Procedure

The study was part of an ongoing twin-family study of health-related characteristics, personality, and behavior in the Nether-lands. The subjects were registered with the Netherlands Twin Registry (NTR; Boomsma et al., 2006). Starting in 1991, adolescent and adult twins have been recruited through city councils. In the past 10 years the NTR has also recruited adult twins through appeals in the media, internet, and through the yearly NTR newsletter [Boomsma et al., 2006]. For this study, we assessed a sample of Dutch twin pairs (mean age = 27.5, SD = 12.21) who reported on their SHSB every 2–3 years for six sampling periods between 1991 and 2009.

Twin zygosity was determined from DNA polymorphisms for 31% of the twin pairs, or, when DNA was not available, from survey questions. Longitudinal surveys in twins and their parents included a number of items for zygosity assessment. The correspondence between zygosity based on survey items and on DNA is 97% [Willemsen et al., 2005].

Measures

Self-reported thoughts of self-harm and suicidal behaviors. Individuals reported on their SHSB based on three instruments. The Youth Self Report (YSR; Achenbach and Rescorla, 2001) for age younger than 18 and the Adult Self Report (ASR; Achenbach and Rescorla, 2003) for age older than 18 are two instruments from the Achenbach System of Empirically-Based Assessment (ASEBA). The ASEBA instruments each contain 113 behavioral items to be answered on a 0–2 scale. Two items from the YSR or ASR relate to SHSB—“18. I deliberately try to harm myself or commit suicide” and “91. I think about killing myself”. While not ideal, because Item 18 conflates deliberate self-injury with attempts to commit suicide, use of only Item 91 would include only suicidal ideation and not attempts. YSR or ASR scores were obtained at timepoints 1, 3, 4, 5, and 6. At timepoints 2 and 4, participants also completed the Beck Depression Inventory (BDI; Beck et al., 1996) which asks participants to choose among a set of four statements to indicate the one that reflects their thoughts and feeling best ranging from “I don’t have any thoughts about harming myself” to “I would kill myself if I could”. Each measure asks that the participants rate their thoughts and feelings over the previous 6 months. Because of the low incidence of a response other than zero to these items, we combined all timepoints and all scales to create a composite SHSB score for each twin which reflects whether an individual had at any sampled timepoint during the study. While this does not allow for taking advantage of the longitudinal design of the study, it does increase power for detecting effects between twins and adds to likelihood of capturing a particular timepoint where a vulnerable twin expressed SHSB. Additionally, we obtained the first age at which the behavior was reported (or, if no SHSB were ever reported, the last age at which the participant returned a survey was recorded). Linear and quadratic effects of age were used as covariates, correcting the prevalence of SHSB for age differences in the time to expression of the SHSB between participants. Because there have been two reported age windows for increased suicidal ideation (teenage and older adult) the quadratic term was also included. Age was entered as a z-score into the threshold equation as β1 × [z(age)] for the linear term and β2 × [z(age)]² for the quadratic term.

Statistical Analyses

Genetic analysis of the data made use of a threshold model [Falconer, 1965] in which the dichotomous variable is seen as the expression of an underlying continuous risk distribution called “liability”. We estimated the threshold of the liability distribution that divided the sample into “affected” and unaffected subjects. All analyses were carried out in Mx [Neale et al., 2006]. Twin correlations were estimated for the liability for SHSB and based on the pattern of the correlations in MZ and DZ twins we fitted several different models of familial resemblance to the data. Tests for quantitative sex differences were carried out by constraining heritability estimates to be the same for men and women. Tests for qualitative sex differences were performed by testing whether the genetic correlations in dizygotic opposite sex differed from 0.5. If this correlation is significantly lower than 0.5, there is evidence that different genes are expressed in men and women.

The relative contributions of genetic and environmental factors for individual differences to liability of SHSB can be inferred from the different level of genetic relatedness of MZ and DZ twins [Neale and Cardon, 1992]. The variance may be due to additive genetic (A) factors, non-additive genetic (D) factors, shared environment (C) effects or non-shared environment (E) effects. The genetic factors are correlated 1.0 in MZ twins, as they genetically identical. For DZ twin, the additive genetic factors are correlated 0.5, because DZ twins share on the average half of their segregating genes. The genetic effects due to non-additive effects are correlated 0.25 in DZ twins. The shared environment (C) is defined as those environmental influences that are similar for family members, thus the shared environmental factors correlate 1.0 in both MZ and DZ twins. E or non-shared environment is by definition, uncorrelated, and also absorbs all uncorrelated error. If the pattern of twin
correlations is such that the MZ correlation is less than twice the DZ correlation then models that test for A, C, and E are pursued. If the pattern of twin correlations is such that the DZ correlation is smaller than 1/2 the MZ correlation then ADE models are considered. The choice between fitting C or D must be based on inspection of twin correlations because estimating C and D at the same time is not possible in a design using only data from MZ and DZ twins reared together.

All model fitting was performed on raw data with Mx [Neale et al., 2006]. ADE and/or ACE models were fit first, and then the significance of the A, D, and C factors was tested by dropping the variance components, using a likelihood-ratio test. When comparing nested models, a change in the −2 log-likelihood between the models is distributed as a chi-square with degrees of freedom equals to the differences in df between the models. A significant difference (P < 0.05) when relaxing a constraint means that this constraint cannot be relaxed. We also computed likelihood-based 95% confidence intervals [Neale and Miller, 1997]. More technical details of genetic model-fitting analyses are reviewed elsewhere [Neale and Cardon, 1992].

RESULTS
Prevalence and Twin Correlations
The numbers of individuals, by zygosity group, who reported SHSB are presented in Table I. Summing for any time over the sampling period resulted in a prevalence of between 6–12% of the sample reporting SHSB, depending on sex and zygosity.

Table I also summarizes twin correlations, which were obtained from the fully saturated threshold model (see Table II). As demonstrated in Table II, the best fitting model allowed for equating all twin 1 and twin 2 thresholds to be equal, MZ and DZ thresholds to be equal within the same sex and DZ thresholds to be the same as the DOS members of the same sex. Thresholds across the sexes were different. These constraints were then retained in the genetic model.

In men, MZ correlations were more than twice as large as the DZ correlations, indicating the need to model the influence of non-additive genetic factors. In women, the MZ correlations were less than twice as large as DZ correlations, indicating the need to model possible influence of shared environmental factors. There were positive effects of both age and the square of age on the thresholds with increased likelihood of SHSB with increasing age, especially in women.

Genetic Model Fitting
A summary of the genetic model-fitting results is given in Table III. An ADE model was fit for males and an ACE model for females. For the model in women, dropping C did not significantly worsen the model fit but dropping A did. For the model in men, dropping D did not significantly worsen the model fit but dropping A did. So, an AE model was the best fitting model for both males and females. Additive genetic and unique environmental variance components in men and women were different, however, indicating that while there were no qualitative differences in the genetic structure of SHSB in men and women, there are quantitative sex differences in heritability. Allowing for the DOS twin correlation to be different from 0.5 resulted in a point estimate that did not differ from 0.5 (0.67 with 95% CI 0.41–0.99), suggesting an absence of qualitative sex differences between males and females.

For women, additive genetics explained 74% of the variance and 26% was explained by unique environment and estimation error. For men, additive genetics explained 45% of the variance and 55% of the variance was explained by unique environment and estimation error. The confidence intervals are provided in Table IV.

DISCUSSION
We aimed to extend upon prior twin studies by analyzing a large enough sample that included male and female monozygotic and dizygotic twin pairs, to determine whether there are sex differences in the genetic architecture of self-reported thoughts of self-harm and suicide. We report that SHSB are relatively common (6–12%) and, for this phenotype with the caveats listed above, the genetic architecture is not qualitatively different between males and females. Our data indicate that additive genetic and unique

<table>
<thead>
<tr>
<th>Twin type (n complete pairs)</th>
<th>Twin</th>
<th>Available suicide data</th>
<th>Prevalence</th>
<th>Mean age (SD)</th>
<th>Twin correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZM (755)</td>
<td>1</td>
<td>870</td>
<td>0.07</td>
<td>27.3 (12.8)</td>
<td>0.47 (0.25, 0.65)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>847</td>
<td>0.06</td>
<td>26.9 (12.4)</td>
<td></td>
</tr>
<tr>
<td>DZM (544)</td>
<td>1</td>
<td>634</td>
<td>0.11</td>
<td>25.0 (11.1)</td>
<td>0.04 (−0.21, 0.28)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>620</td>
<td>0.08</td>
<td>25.1 (10.7)</td>
<td></td>
</tr>
<tr>
<td>MZF (1499)</td>
<td>1</td>
<td>1621</td>
<td>0.09</td>
<td>30.4 (13.7)</td>
<td>0.72 (0.63, 0.80)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1624</td>
<td>0.10</td>
<td>30.3 (13.5)</td>
<td>0.72 (0.63, 0.80)</td>
</tr>
<tr>
<td>DZF (855)</td>
<td>1</td>
<td>1001</td>
<td>0.11</td>
<td>28.1 (12.9)</td>
<td>0.44 (0.29, 0.59)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>976</td>
<td>0.10</td>
<td>27.9 (12.0)</td>
<td>0.44 (0.29, 0.59)</td>
</tr>
<tr>
<td>DOS (1134)</td>
<td>1</td>
<td>1270</td>
<td>0.09</td>
<td>24.84 (10.20)</td>
<td>0.37 (0.23, 0.50)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1545</td>
<td>0.12</td>
<td>25.4 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Age at which subject first reported suicidal thoughts and behavior or age at which participant last reported, if never reporting suicidal thoughts and behavior.*
environmental factors account for both male and female SHSB. However, we found statistically significant evidence (the 95% confidence intervals around the additive genetic estimates between males and females do not overlap) that the genetic influences on SHSB in females was 1.6 times (74% vs. 45%) greater than in males. While others have reported differences in the magnitude of additive genetic and unique environmental influences for suicidal thoughts and behaviors between males and females, this is the largest study to report substantially greater genetic influence on female SHSB. Further, we account for many, but certainly not all, of the concerns of Voracek and Loibl [2007] who worried about residual problems with twin research on suicide including: (1) Questions of zygosity (in this study zygosity was determined using molecular genetic in addition to questionnaire approaches, at least on a subset of the sample, (2) recruiting biases (in this study all twin pairs were recruited from a general population twin sample through the Netherlands Twin Registry) and reporting effects (in this study all data were collected in the same way using a standardized questionnaire in which SHSB were only a small part of the report), (3) age effects without correction in the studies (in this study we controlled for age and demonstrated a significant effect of age on the threshold for symptoms), and (4) lack of systematic study of sex differences (in this study we systematically studied the effects of sex). Critically, however, we could not address the concern about conflating non-suicidal self injury with suicidal behavior in this sample (see Limitations, below).

Our findings that the architecture of SHSB in males is equal part genes and unique environment are consistent with what has been reported about suicidal ideation and attempts in males. Suicidal behavior has been reported to be familial in males and males who engage in suicidal behavior are commonly also affected by a unique environmental moderator like loss of a job, loss of a spouse, or injury. Of course, some of these risk factors tend to co-occur along with psychiatric and substance use disorders which have a high additive genetic risk in men [Hawton and van Heeringen, 2009].

Our findings in women are also consistent with prior findings on SHSB. We report that the primary influence of female SHSB is due to additive genetic factors, suggesting that the most common reason for familiality of SHSB in female relatives is the genes that they share. Glowinski et al. [2001] importantly noted that a child’s increased genetic vulnerability to suicide attempt is associated with increased environmental vulnerability as well. In that work, various genetic and environmental conditions that correlated with a higher risk for attempted suicide were also conditions conferring risk for offspring abuse. They offered the example of parental alcoholism,
reported by nearly half (46.1%) of the suicide attempting probands [Glowinski et al., 2001]. According to other findings from the same group offspring suicidality in children of alcohol-dependent fathers cannot be exclusively attributed to genetic factors as environmental factors are likely responsible as well [Glowinski et al., 2004]. Additionally, suicidal ideation and suicide plan held significant relationships with non-alcohol substance abuse or dependence by the father. These findings are also consistent with the report that cluster B traits are mediators of suicidal behavior [McGirr et al., 2009]. It is necessary to acknowledge that each of these factors may not be exclusively environmental, but rather mediated by or inextricably linked to genetics [Brent et al., 2002; Lynskey et al., 2004; Connor and Rueter, 2006; Brodsky et al., 2008] and that additive genetic effects in twin models from one generation can include gene and environment interaction effects as well as direct additive genetic effects.

The work reported here is consistent with findings of increased suicidal ideation with increasing age. At first, it appears that this might be driven by the large age span (11–90). However, while the age span is large, the variance is actually quite low with mean age = 27.5 and SD = 12.21, meaning that 70% of the sample fell between the ages of 15–40, making this mainly a study of young adults, but taking into account the increasing likelihood of self-reported thoughts of self-harm and suicidal behaviors with increasing age.

This work is not without limitations. We were unable to respond to the concerns of previous work concerning phenotypic confounds between non-suicidal self-injury and suicidal behavior because we were limited to the use of the available questionnaires (BDI and YSR/ASR) as measures of self-harm thoughts and behavior. In a large twin register, there is a trade-off between burden of data collection and detail of the reporting. The items used here are relatively nonspecific indicators of self-harm thoughts and behavior which include suicidal thoughts and behavior as well as non-suicidal self-injury. However, it remains an important goal to further examine specific suicidal ideation as separable from non-suicidal self-injury and those studies are ongoing.

A second possible disadvantage to the approach taken here is that despite data being collected in multiple waves, we did not examine thoughts of self-harm and suicide in a longitudinal fashion, but rather, by design, created the largest cross-sectional data set that the data allowed and in this way use the whole sample to give a population-based estimate of thoughts of self-harm and suicide. Notably, this approach led to an estimate across the sample of endorsing self-harm thoughts and suicidal behaviors of 6–12% which is markedly similar to the prevalence of endorsed suicidal ideation in an epidemiological study of the Netherlands and 16 other countries [Nock et al., 2008]. Lastly, while this is a community twin sample, it is not a weighted general population epidemiological sample and there are some non-responders at various waves of data collection. Examination of the demographics demonstrates more females responding than males, consistent with the recruitment in the NTR [Boomsma et al., 2006]. Previous work in the NTR has demonstrated that while it is the case that non-responders to the surveys have slightly higher measures of risk behavior, examination of these increases are small, leaving the surveys to be relatively unbiased in their assessment of the scores in the general population [Distel et al., 2007].

In conclusion, these results suggest that self-reported thoughts of self-harm and suicidal behavior are common, influenced by genetic factors in men and, to an even greater degree, in women. Individuals at risk for suicide must be identified early. Assessment of family history, particularly in females, and risk environments will continue to be important targets. Doubtless, early offspring support must be provided for those with parental suicidality and psychopathology [Mittendorfer-Rutz et al., 2008], with added emphasis on risk assessment for relatives of completed suicides. Clinical treatment should attend to both parents and offspring, with considerations of the complete family history of suicidality and self-harming behavior. In addition to additive genetics factors, there are unique environmental influences to consider in the expression of thoughts of SHSB.

Our findings, viewed through the lens of epigenetics, particularly the work of McGowan et al. [2009], provide a guide for possible next steps in the molecular genetic study of SHSB. Given the contribution of environmental factors to SHSB it may well be that these factors, whatever they are (e.g., abuse, neglect, concentrated poverty), may lead to epigenetic changes that in turn increase the risk for thoughts of self-harm and suicide. This epigenetic cascade gives us a window on the biology of suicide and self-harm by providing a possible explanation of how the environment may affect the genome which then may play a role in suicidal behavior. Given the phenotypic caveats of the current work, one should not view the current results as the definitive study of the genetics of the narrower category of suicide, but as another important clue in the examination of how genes and environment contribute to self-harm and suicidal thoughts which may be investigated further through phenotypic refinement and examination of epigenetic mechanisms.

### TABLE IV. Estimates of Variance Components, Thresholds, and Regression Weights (for Fixed Effects of Age and Age² on the Thresholds) With 95% Confidence Intervals Around the Estimates

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>E</th>
<th>Threshold</th>
<th>β (age)</th>
<th>β (age²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.45</td>
<td>0.55</td>
<td>1.45</td>
<td>0.01</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>(0.28, 0.61)</td>
<td>(0.387, 0.720)</td>
<td>(1.39, 1.51)</td>
<td>(−0.01, 0.03)</td>
<td>(0.18, 0.32)</td>
</tr>
<tr>
<td>Women</td>
<td>0.74</td>
<td>0.26</td>
<td>1.32</td>
<td>0.03</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>(0.65, 0.81)</td>
<td>(0.19, 0.35)</td>
<td>(1.27, 1.37)</td>
<td>(0.02, 0.03)</td>
<td>(0.34, 0.45)</td>
</tr>
</tbody>
</table>

Note. Age, age at which subject first reported suicidal thoughts and behavior or age at which participant last reported, if never reporting suicidal thoughts and behavior which was converted into a Z-score before entering into the analysis.


