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Genetic analyses of DSM-IV nicotine withdrawal in adult twins

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ABSTRACT

Background. We examined whether there are genetic influences on nicotine withdrawal, and whether there are genetic factors specific to nicotine withdrawal, after controlling for factors responsible for risk of progression beyond experimentation with cigarettes and for quantity smoked (average number of cigarettes per day at peak lifetime use).

Method. Epidemiologic and genetic analyses were conducted using telephone diagnostic interview data from young adult Australian twins reporting any cigarette use (3026 women, 2553 men; mean age 30 years).

Results. Genetic analysis of the eight symptoms of DSM-IV nicotine withdrawal suggests heritability is intermediate for most symptoms (26–43%), and similar in men and women. The exceptions were depressed mood upon withdrawal, which had stronger additive genetic influences in men (53%) compared to women (29%), and decreased heart rate, which had low heritability (9%). Although prevalence rates were substantially lower for DSM-IV nicotine withdrawal syndrome (15.9%), which requires impairment, than for the DSM-IV nicotine dependence withdrawal criterion (43.6%), heritability was similar for both measures: as high as 47%. Genetic modeling of smoking more than 1 or 2 cigarettes lifetime (‘progression’), quantity smoked and nicotine withdrawal found significant genetic overlap across all three components of nicotine use/dependence (genetic correlations = 0.53–0.76). Controlling for factors associated with risk of cigarette smoking beyond experimentation and quantity smoked, evidence for genetic influences specific to nicotine withdrawal (up to 23% of total variance) remained.

Conclusions. Our results suggest that at least some individuals become ‘hooked’ or progress in the smoking habit, in part, because of a vulnerability to nicotine withdrawal.

INTRODUCTION

Cigarette smoking remains the single greatest preventable cause of death in the USA (CDC, 2005a), and severity of nicotine withdrawal (NW) symptoms is believed to contribute to smoking cessation failure (Cummings et al. 1985a, b; West et al. 1989; Carmody, 1992; Shiffman et al. 1997; Piasecki et al. 1998, 2000, 2003). Gaining a greater understanding of both phenotypic and genetic characteristics of NW may be useful in decreasing morbidity and mortality in heavily dependent and relapsing smokers, if findings can be successfully applied to smoking-cessation interventions. Genetic influences play an important role in initiation of smoking (Heath et al. 1993; Heath & Madden, 1995; Li et al. 2003; Madden et al. 2004) and an even greater role in persistence of smoking (Heath & Madden, 1995; Madden et al. 1999) and nicotine dependence (Kendler et al. 1999; True et al. 1999; Lessov et al. 2004; Maes et al. 2006).
Heritability estimates for smoking persistence range from 53% to 71% (Kaprio & Koskenvuo, 1988; Heath & Martin, 1993; Heath & Madden, 1995), and for nicotine dependence range from 56% to 72% (Kendler et al. 1999; True et al. 1999; Lessov et al. 2004; Maes et al. 2004). Withdrawal plays a central role in some theories of dependence (e.g. the dependence syndrome conceptualized by Edwards & Gross, 1976; Shiffman et al. 2004). Genetic research on risk for withdrawal symptoms on cigarette reduction can address the extent to which differences in withdrawal vulnerability are potential mediators of the powerful genetic influences that have previously been reported for other components of smoking behavior (Heath et al. 1993; Heath & Madden, 1995; Madden et al. 1999; Li et al. 2003; Madden et al. 2004).

In an effort to refine the phenotype of NW, Madden et al. (1997) examined lifetime NW in a survey of an older Australian cohort of adult female twins. Using latent class analysis they found three NW severity classes. However, they did not have adequate power to test for genetic influences on the latent classes. Similar phenotypic results were recently found using the Vietnam Era Twin Registry (Xian et al. 2005). In addition, in this population of male twins, Xian and colleagues (2003, 2005) reported significant genetic influences on NW, viewed as continuous factor scores (29.7% heritability in regular smokers) or as latent classes (31%). In addition, a modest genetic correlation between withdrawal and failed cessation ($r_A = 0.31–0.37$) was found (Xian et al. 2003, 2005). One limitation of this study was that the analyses excluded pairs where both twins did not try to quit cigarettes. Multivariate genetic analyses of nicotine-dependence symptoms in a young adult Australian twin cohort (Lessov et al. 2004) have also provided evidence for significant genetic variance in NW vulnerability (53% heritability in ever smokers), and demonstrated that most, but not all, genetic risk contributing to the onset of NW was shared with other nicotine-dependence symptoms.

Important areas of uncertainty remain concerning the genetics of NW vulnerability. At the most basic level, there have been no reports of the heritability of individual symptoms of NW. Also unclear is the degree of genetic overlap between the initiation of regular cigarette smoking and NW vulnerability. Given the evidence for genetic influences on the initiation of smoking (Heath et al. 1993; Heath & Madden, 1995; Li et al. 2003; Madden et al. 2004), various models, with varying limitations (e.g. Heath et al. 2002), have been used to examine the overlap of genetic influences on initiation of smoking, and genetic influences on outcome measures including persistence of smoking (Eaves & Eysenck, 1980; Heath, 1990; Heath & Martin, 1993; Madden et al. 1999; Heath et al. 2002), quantity smoked (Koopmans et al. 1999), and nicotine dependence (Kendler et al. 1999; Maes et al. 2004), but these methods have not been applied to the case of NW.

Our goals in this paper were, therefore, to examine in both women and men: (1) genetic and environmental influences on individual DSM-IV symptoms, DSM-IV withdrawal criteria for nicotine dependence, and DSM-IV-defined nicotine withdrawal syndrome (NWS), and (2) the extent to which the same genetic and environmental factors underlie the transitions from smoking beyond experimentation with cigarettes, quantity smoked regularly and vulnerability to NW.

**METHOD**

**Participants**

*The 1989 Australian Adult Twin Cohort*

Participants were male and female twins born 1964–1971 from the Australian Twin Registry who were first surveyed by mailed questionnaire in 1989 and later interviewed between 1996 and 2000. These twins were volunteered by their parents, in response to media appeals and appeals through the Australian school system in 1980–1982 (see Heath et al. 2001; Knopik et al. 2004 for further details of this sample). Participants were interviewed independently by telephone using structured diagnostic assessments for DSM-IV (APA, 1994) nicotine dependence, alcohol dependence, major depression, panic disorder, and childhood conduct disorder, as well as non-diagnostic assessments of social anxiety, suicidality, a screen for bipolar disorder, and a detailed history of consumption of alcohol, cigarettes, and other forms of tobacco, and illicit drugs. The interview was a modified version of the Semi-Structured Assessment on
the Genetics of Alcoholism (SSAGA; Bucholz et al. 1994) and the smoking section was modified from the Composite International Diagnostic Interview (CIDI; Cottler et al. 1991). Telephone interview data were available from a total of 6257 individual twins (3454 women and 2803 men; 1496 monozygotic (MZ) female twins, 1140 MZ male twins, 1136 dizygotic (DZ) female twins, 941 DZ male twins, and 1544 unlike-sex twins). As is typical of a volunteer twin sample, the sample contained a higher proportion of MZ female twins than would be expected from the natural twinning ratio. At the time of interview, all respondents ranged in age from 24–36 years old (mean age = 30). In the present study, analysis was limited to individuals who had ever tried cigarettes (and had data on smoking progression: n = 5579, 54% female) and twin pairs where both twins had used cigarettes (and had data on smoking progression: 557 MZF, 418 MZM, 423 DZF, 333 DZM, and 559 DZ unlike sex pairs).

**Measures**

*Progression beyond experimentation with cigarettes (smoking progression)*

Participants who endorsed ‘trying’ cigarettes (at least one puff) were asked to further describe their lifetime smoking behavior as: (1) I have only smoked one or two times ‘just to try’; (2) I have only smoked occasionally, never as often as one day a week for three weeks or more; (3) I have smoked as often as one or two days a week (but never more than one or two days a week) for a period of three weeks or more, or (4) I have smoked daily, or nearly every day, for a period of three weeks or more. Smoking progression was coded as ‘0’ if they endorsed smoking only one or two times ‘just to try’ and was coded as ‘1’ if participants reported smoking more than twice. Never-smokers were not included. Given the age of the sample (median age 30), and the relatively low prevalence of late-onset smoking, we would not expect statistical censoring to be an issue for analyses.

*Quantity smoked*

Quantity smoked was coded as ‘0’ for individuals who reported smoking more than two times but less than 100 times in their lifetime. Individuals who reported smoking 100 or more times were asked in reference to the period of time when they smoked the most. ‘How many cigarettes did you smoke on a typical day, on those days when you smoked?’ Quantity smoked was coded as ‘1’ if they reported smoking between 1–10 cigarettes per day (cpd), ‘2’ for 11–15 cpd, ‘3’ for 16–19 cpd, ‘4’ for 20–25 cpd, and ‘5’ for 26 or more cpd. Individuals who had only smoked once or twice were coded as missing on the quantity smoked variable.

The definition of quantity smoked used in our analyses (a 6-level ordinal variable) was determined by the following criteria (Heath et al. 2002): (1) the variable must be at least three levels, and at least two of those levels should not have structurally missing data on the third outcome dimension (NW), and (2) the variable must fit a single dimension liability model (Eaves & Eysenck, 1980). The quantity smoked variable detailed above fit these criteria. In all analyses, individuals who never smoked more than twice were coded as missing for quantity smoked.

*NW*  
Individuals who reported smoking at least 100 cigarettes lifetime were asked ‘about problems they might have had in the first 24 hours after they stopped or cut down or when they were unable to smoke’. Only 48 out of 3158 smokers reported never stopping or cutting down on their smoking for at least 24 hours, and these individuals were not asked questions concerning NW and were coded as missing for these items. The different measures of DSM-IV NW considered were as follows: (1) Participants were queried as to whether they experienced each of the eight DSM-IV NW symptoms: irritable or angry, nervous, restless, trouble concentrating, decreased heart rate, increased appetite, feel down or depressed, and trouble sleeping. (2) Individuals were classified according to whether they met criteria for DSM-IV NW using substance dependence criteria, i.e. endorsement of four or more of the symptoms within 24 hours or smoking cigarettes again to relieve or avoid withdrawal symptoms. (3) Individuals were classified by DSM-IV NWS criteria, i.e. the endorsement of four or more of the NW symptoms within 24 hours with impairment (that is the symptoms caused significant distress or
impairment in social, occupational or other important area of functioning). Individuals who reported smoking fewer than 100 times lifetime were not asked questions related to NW. Thus, all measures of NW were set to missing for these individuals in all analyses. The use of 100 or more cigarettes lifetime is widely used to define a lifetime history of adult cigarette smoking (e.g. CDC, 2005b).

**Statistical approach**

Prevalence rates for smoking progression, quantity smoked and each measure associated with NW were estimated separately for women and men using SAS software (SAS, 1999). In order to determine whether the NW items could be represented by a single latent factor, factor analyses were also conducted separately for women and men in SAS (SAS, 1999). Given the missing data structure inherent in the derived measures, we computed conditional sample size estimates across the stages, in order to assess the availability of adequate numbers in each response category across the three dimensions. Wald $\chi^2$ tests of the significance of regression parameters were generated in STATA (StataCorp, 2003) using the robust variance estimator to control for non-independence of measures.

Univariate genetic models (Eaves et al. 1978; Neale et al. 2002) were fitted for each categorical measure by the method of maximum likelihood, using the ordinal data option in Mx (Neale et al. 2002) to estimate the proportion of the total variance in each measure that could be explained by additive genetic factors (A), environmental influences shared by members of a twin pair (C), and non-shared environmental influences (E).

For multivariate genetic analyses, we used a modification of a recently developed two-stage modeling approach (Heath et al. 2002), which is an extension of earlier modeling methods (e.g. Kendler et al. 1999), that allows for estimation of the magnitude of genetic and environmental correlations between different stages of smoking behaviors, when the earlier stages of smoking are more clearly defined as multi-category rather than binary variables. The two-stage modeling approach was developed to handle a class of problems where some phenotypes can only be assessed conditional on values of another phenotype (e.g. tobacco withdrawal cannot meaningfully be characterized in individuals with minimal tobacco exposure). Simply limiting analysis to twin pairs concordant for more than minimal levels of tobacco exposure would lead to biased estimates of genetic and environmental parameters if there were overlap between genetic influences on exposure, and genetic influences on outcome. While various somewhat arbitrary conditions can be imposed to ensure that a bivariate normal genetic model is identified when the first ‘unconditional’ dimension is assessed as a binary variable, these can be avoided (i.e. the full bivariate normal or multi-variate normal genetic model estimated) provided that the unconditional dimension can be modeled as a multiple-category trait, with non-missing data on the second dimension for two or more categories on the first dimension. Since the model is dependent upon normal distribution theory, this approach does, however, depend upon finding an acceptable fit of the first unconditional dimension to a normal liability (‘multiple threshold’) model. This method thus allows for more accurate estimation of genetic and environmental correlations, in part because persons missing in one dimension (e.g. experimenters and occasional smokers who have never smoked are incorporated more systematically into the model.

For the present study, we extended the two-stage model to a three-stage trivariate genetic analysis, including smoking progression (beyond trying cigarettes), quantity smoked and NW. Since 89% of respondents reported a history of cigarette use, limiting analysis to pairs concordant for any cigarette use would not be expected to seriously bias estimates of effects in subsequent stages of smoking. Since it was also not possible to define a multi-level measure of smoking progression (beyond experimentation), we defined this as a binary variable, and fixed to zero the non-shared environmental correlations between this variable and the two other smoking measures, in order to identify the model. Since estimates of non-shared environmental variance in twin data are only weakly correlated with estimates of additive genetic and shared environmental variance, we would expect [and have confirmed by simulation (Heath et al. 2002)] that this approach will yield estimates of genetic and shared environmental variances that very closely approximate those obtained under a full model when such a model is identified and
estimates of genetic correlations that are only slightly reduced (0.00–0.20; Heath et al. 2002). For those who progressed beyond experimentation, we defined a second quantity dimension, which was undefined (and therefore set to missing) in those who smoked once or twice. For those who smoked regularly (100 or more times), we defined a third NW variable, with experimenters and occasional smokers both set to missing on this third variable (Fig. 1). Extension to a quadrivariate four-stage model was precluded by evidence of heterogeneity of twin-pair concordance for the earliest stages of smoking as a function of simultaneous versus separate smoking initiation (Pergadia et al. 2006), inability to fit a multiple threshold model to the initiation stage, and limited power to resolve competing hypotheses about the overlap of genetic and environmental influences on initiation versus later stages of smoking. The issue of power has not been generally appreciated: a corollary of the very high MZ pair concordance for any smoking is that there are few discordant MZ pairs, hence almost no power to determine whether overlap of familial influences in initiation (ever use) and later stages of smoking is due to genetic or shared family environmental influences. Genetic and environmental variances and correlations were estimated by maximum likelihood using Mx software (Neale et al. 2002) under a multiple threshold model which assumes a continuous normal distribution of liability with distinct thresholds superimposed. The goodness-of-fit of the full model was compared, by likelihood ratio \( \chi^2 \) test, to submodels which (i) fixed genetic parameters to zero (testing the significance of genetic effects), or (ii) fixed shared environmental parameters to zero (testing the hypothesis that there is no overall effect of environmental factors shared by twin pairs reared together).

**RESULTS**

Principal factor analyses identified a single factor solution in both women and men for the DSM-IV NW items. Decreased heart rate and increase in appetite had only modest loadings in women (0.0-0.24 respectively) and men (0.0-0.28). All other item loadings ranged between 0.44-0.67. Table 1 shows the prevalence rates for smoking progression, quantity smoked, and DSM-IV nicotine withdrawal. cpd, Cigarettes per day.

![Diagram](image-url)
cigarettes per day than female twins (Wald $\chi^2_1 = 75.3$, $p < 0.001$). For the DSM-IV NW symptoms prevalence rates ranged from a low of 13.0% for decreased heart rate to a high of 60.2% for restlessness. Rates were equivalent across women and men, except for depressed mood which was significantly elevated in women (27.0%) compared to men (18.7%, Wald $\chi^2_1 = 27.0$, $p < 0.001$). Subsidiary analyses found that except for nervousness, rates of all other reported NW symptoms were also significantly higher in individuals who persisted in smoking (reported smoking in the last 6 months; OR 1.2–1.8). Rates for NW (44.2%, 43.0%) and NWS (17.0%, 14.7%) did not differ across women and men, respectively. However, rates of NWS were three times lower than NW. While over 40% of smokers reported experiencing four or more symptoms of NW, at some point in their life when they quit or cut down on smoking, these symptoms were perceived to have caused significant impairment in only approximately one-third of these cases.

Conditional sample size estimates across the stages of smoking progression, quantity smoked and NW, and corresponding percentages, are depicted in Fig. 1. For example, there were 79% ($n = 4390$) of experimenters who reported smoking beyond experimentation. Experimenters who did not progress in smoking (21%, $n = 1189$) were missing data on both quantity smoked and NW. Of those who progressed in smoking, 28% ($n = 1231$) did not smoke 100 or more cigarettes lifetime and were missing data on NW. Of individuals who had data for NW symptoms, rates of meeting criteria for DSM-IV nicotine withdraw ranged from 25% in individuals who smoked 1–10 cpd to 62% in individuals smoking $\geq$ 26 cpd. Estimates for NWS were approximately one-third of that for NW. Phenotypic correlations between quantity smoked and NW and NWS were 0.44 and 0.43, respectively, and could be constrained across males and females (NW: $\chi^2_3 = 6.4$, $p = 0.09$; NWS: $\chi^2_3 = 2.5$, $p = 0.47$).

Univariate genetic analyses of smoking progression (conditioned on smoking once or twice), quantity smoked, and NW measures (conditioned on smoking 100 or more times), are shown in Table 2. Included in the table are standardized maximum-likelihood estimates of additive genetic (A), shared environmental (C), and non-shared environmental variances (E) and their 95% confidence intervals (CI). Estimates of shared environmental variance under the full ACE model were in all cases zero or nearly so. However, for four variables (nervousness, decreased heart rate, trouble
sleeping, and in women only, depressed mood) it was not possible to discriminate between AE and CE models, i.e. either A or C could be dropped, but not both. There were no cases where inclusion of non-additive genetic effects significantly improved upon the AE model. The non-shared environmental variance for decreased heart rate was very high (91%) and additive genetic influence correspondingly low (9%). For all other withdrawal symptoms, heritability estimates were intermediate in magnitude (26–53%). Significant heterogeneity of genetic and environmental parameters across gender was observed only for a single symptom, depressed mood ($\chi^2 = 11.9, p = 0.04$) with higher heritability observed in males. Importantly, for the six-level quantity smoked variable, the multiple threshold gave an adequate fit to the data ($\chi^2 = 135.9, p = 0.10$).

Fig. 2 depicts the best-fitting three-stage model for genetic and environmental effects on smoking progression and the conditional phenotypes of quantity smoked (in those who smoked once or twice) and NW (in those who smoked at least 100 times). We were able to simplify our initial trivariate ACE models, by constraining parameters to be equal across gender ($\chi^2 = 23.2, p = 0.11$), and then fixing all C parameters to zero ($\chi^2 = 6.4, p = 0.38$). Significant genetic correlations were found between: (1) smoking progression (beyond experimentation) and quantity smoked: $r_{A1} = 0.72 (0.60–0.83)$; (2) smoking progression and NW: $r_{A3} = 0.53 (0.26–0.77)$; and (3) quantity smoked and NW: $r_{E3} = 0.17 (0.04–0.29)$. Overall, 45.1% of the variance in risk for NW was found due to genetic factors, with 19.3% specific to NW, 13.4% common to smoking progression, and 12.4% common to quantity smoked (controlling for smoking progression). Similar results emerged using DSM-IV NWS where the 47.4% of the total variance in NWS due to genetic factors could be decomposed into: 23.3% specific to NWS, 8.6% common to smoking progression and 15.5% common to quantity smoked.

**DISCUSSION**

Several important findings emerge from our analyses. Consistent with previous studies...
(Svikis et al. 1986; Breslau et al. 1992), there was remarkable consistency across gender in rates of reporting NW symptoms, and in the magnitude of correlations of NW with quantity smoked, in regular smokers, despite men smoking more heavily. It is possible that average nicotine exposure may actually be more similar across gender, given that men are on average larger and overall body clearance of nicotine is also on average greater (Zevin & Benowitz, 2000). Only for a single symptom, depressed mood upon withdrawal, was a higher prevalence observed in female than in male regular smokers (27% v. 19%). There was also consistency across gender in the magnitude of genetic and environmental influence on risk of individual withdrawal symptoms, and on risk of NW or NWS, with most estimates of intermediate magnitude (26–43%). The single exception was depressed mood upon withdrawal, which appeared to have stronger additive genetic influences in men (53%) compared to women (29%), an un-anticipated finding for which we do not have an explanation. While depressed mood upon withdrawal was associated with a history of major depression (OR 2.3), this association did not vary by gender. To our knowledge, this is the first report on the differential heritability of individual NW items. Although prevalence rates were substantially lower for DSM-IV NWS compared to DSM-IV NW (using substance dependence criteria) heritability estimates were similar for both definitions: 45% for NW and 47% for NWS, and not substantially greater than the estimates (30–31%) previously reported by Xian and colleagues (2003, 2005) using summary measures of DIS-based NW in male veterans. Our finding that 61% of the total variance in smoking beyond experimentation may be due to additive genetic influences is also within the range of previous estimates for regular smoking in adults from the USA and Australia (Heath et al. 1993), while the estimate of 57% for quantity smoked is somewhat lower than the estimate of 85% reported by Koopmans et al. (1999) in an adolescent/young adult Dutch twin sample. This difference might be due to differences in the age ranges used in these two samples, cultural differences, or differences in phenotypic definition (e.g. they used a three-level variable). Evidence suggests a possible candidate gene for quantity smoked might be the CYP2A6 with 3-hydroxycotinine as a potential endophenotype (Benowitz et al. 2003).

The phenotypic factor analyses conducted in this study suggested that decreased heart rate and increased appetite, when assessed by retrospective self-report, show only weak correlation with other DSM-IV NW symptoms. In the case of decreased heart rate, genetic analyses revealed little evidence for familiality. When we redid analyses (not reported under Results above), excluding these two items, estimates of prevalence of NW in regular smokers (39% in women, 36% in men) and heritability (41%) changed only slightly.

We presented here the first analyses of the overlaps between genetic influences on smoking progression, quantity smoked, and NW. We used a hierarchical modeling procedure to examine the genetic overlap between the conditional phenotypes of NW (which could be assessed only in those who had become regular smokers), quantity smoked (assessed only in those who had progressed beyond experimentation) and progression beyond experimentation. A moderate but significant genetic correlation between progression beyond experimentation, and NW (0.53) was observed, as well as a more pronounced genetic correlation between quantity smoked and NW (0.76) controlling for progression. We also found significant genetic variance (19%) that was specific to risk of NW, i.e. not explained by factors that also influenced progression beyond experimentation or quantity smoked. Results were very similar using the more severe NWS phenotype. The genetic overlap that was found between experimentation and withdrawal is important in the context of dependence syndrome models that attribute a key role to withdrawal symptoms in the emergence of dependence. This result raises the possibility that at least some individuals become ‘hooked’ or progress to daily smoking in part because of increased vulnerability to NW symptoms early in their smoking careers.

Our results suggest that genetic influences on quantity smoked per day can account for not much more than one-half (0.76^2 = 58%) of the genetic variance in NW vulnerability. However, interpretation of this result is complicated by the fact that self-report of cigarettes per day is only an imperfect measure of achieved blood nicotine.
levels (Etter & Perneger, 2001). Thus, we cannot exclude the possibility that with better (e.g., biochemical) measures of exposure, a higher genetic correlation would be found. It remains possible, however, that even with more perfect measures of exposure, important genetic differences in withdrawal risk will be found among individuals with very similar exposure histories.

There are several limitations to our findings. NW was assessed retrospectively. Such retrospective self-report assessment is unavoidable for twin study analyses, since limiting an analysis to pairs concordant for current smoking would itself introduce biases to estimates of genetic and environmental effects. Others have found across two separate 48–96 hours’ abstinence periods that self-reported NW symptoms were reliable (0.60–0.87; Hughes et al. 1984; Tate et al. 1993), and that observer reports of NW are significantly associated with self-reports (0.40–0.62; Hughes & Hatsukami, 1986). Nonetheless, the reliability and validity of retrospective self-reports of NW remains to be examined compared to contemporaneous measures. Some DSM-IV NW symptoms appear difficult for individuals to self-report reliably, such as decreased heart rate (Hughes & Hatsukami, 1998). Our analyses raise the possibility that NW could be an informative phenotype to identify genes associated with cigarette use and related problems.

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DECLARATION OF INTEREST

None.

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