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## Retinal Microvessels Reflect Familial Vulnerability to Psychotic Symptoms: A Comparison of Twins Discordant for Psychotic Symptoms and Controls

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## Abstract

Mounting evidence suggests that individuals with schizophrenia have an underlying vulnerability to cardiovascular disease, and a recent study suggested that this vulnerability might be reflected in the retinal microvasculature. The purpose of this study was to test the hypothesis that the retinal microvessels reflect familial vulnerability to psychotic symptoms. Participants were 531 adolescent and young adult twins who took part in the Brisbane Longitudinal Twin Study and the Twins Eye Study in Tasmania. The twins had photographs taken of their retina when they were adolescents or young adults (M age=20.6 years), and retinal vessel diameter was assessed using computer software. The twins completed an assessment of psychosis symptoms approximately six years later. We compared retinal venular diameters of individuals with one or more symptoms of psychosis (n=45), their unaffected co-twins (n=24), and controls (n=462). Individuals with one or more symptoms of psychosis had wider venules (standardized mean=0.29) than controls (standardized mean=-0.04; p=.03), and unaffected co-twins had venular diameters that were intermediate (standardized mean=0.13) between the two groups, suggesting that wide venules may represent a proxy marker of familial vulnerability to psychosis symptoms. Consistent with previous work, there were no differences in arteriolar diameter between individuals with and without symptoms of psychosis. Findings suggest that wide retinal venules may serve as a proxy marker of familial liability to psychosis symptoms. The pathophysiological mechanisms linking psychosis and cardiovascular disease may be operative from early in life, possibly at the level of the microvasculature.

## Keywords

Psychosis; retinal vessel diameter; twin

## 1. Introduction

Individuals diagnosed with schizophrenia are disproportionately affected by cardiovascular and cerebrovascular diseases (Bresee et al., 2010; Carney et al., 2006; Crump et al., 2013; Fan et al., 2013; Hennekens et al., 2005; Lahti et al., 2012; Lin et al., 2008), and their elevated rates of these diseases cannot be fully explained by lifestyle factors, such as smoking or use of antipsychotic medication (Fan et al., 2013; Osborn et al., 2007). Mounting evidence suggests that individuals with schizophrenia may have an underlying liability to cardiovascular disease (Andreassen et al., 2013; Correll et al., 2014; Kohen, 2004; Ryan et al., 2003; Spelman et al., 2007), and a recent study suggested that this liability might be reflected in the retinal microvasculature (Meier et al., 2013).

The retinal microvasculature offers a unique opportunity to visualize the microcirculation in vivo. The condition of the retinal microvessels can be used to gauge the condition of the microvessels in the heart and brain, because the microvasculatures of the retina, heart, and brain are similar (Cheung et al., 2012; Patton et al., 2005). Prior research has shown that the

retinal microvessels are sensitive to a range of cardiovascular risks (Ikram et al., 2012; Sun et al., 2009b), and wider retinal venules (veins) predict risk of coronary heart disease (McGeechan et al., 2009a; Wong et al., 2006b), stroke (Cheung et al., 2013; McGeechan et al., 2009b; Wong et al., 2006b; Yatsuya et al., 2010), cognitive impairment (Shalev et al., 2013), and dementia (de Jong et al., 2011) independently of other cardiovascular risks.

In an initial study of a population-representative cohort from New Zealand (the Dunedin Study), adults diagnosed with schizophrenia were distinguished from other cohort members by wider retinal venules, even after accounting for other cardiovascular risks (high blood pressure, pre-diabetes/diabetes, persistent tobacco dependence) (Meier et al., 2013). Further, adults with symptoms of psychosis and cohort children who exhibited symptoms of psychosis but did not develop schizophrenia had wider venules as adults (Meier et al., 2013), suggesting that wide retinal venules may be related to vulnerability to schizophrenia rather than the disease process itself (Malaspina, 2013). Based on these initial findings, we hypothesized that 1) wide venules may be apparent among adolescents and young adults who experience symptoms of psychosis, and 2) wide venules may be apparent among the unaffected relatives of adolescents and young adults with symptoms of psychosis. We tested these hypotheses in a sample of adolescent and young adult twins.

## 2. Materials and Methods

### 2.1. Participants

Participants were members of the Brisbane Longitudinal Twin Study, an ongoing study of adolescent and young-adult monozygotic (MZ) and dizygotic (DZ) twin pairs and their siblings (Gillespie et al., 2013; Wright and Martin, 2004). As described in detail elsewhere (Gillespie et al., 2013; Wright and Martin, 2004), twins were initially recruited to the study from primary and secondary schools in South East Queensland in 1992, with new twins added at various intervals. All schools in South East Queensland were approached, and all regions in South East Queensland were represented. Comparisons of this sample with other population-based samples suggest that this sample is representative with respect to a variety of traits, including, for example, personality (de Moor et al., 2012) and retinal vessel diameter (Ikram et al., 2010) (Mitchell et al., 2007).

The twins have undergone a variety of phenotypic assessments, including, most recently (and ongoing), an assessment of psychosis symptoms. A subset of participants also completed an extensive eye examination as part of the Twins Eye Study in Tasmania (Mackey et al., 2009; Sun et al., 2009c). Here we report on 531 participants for whom both eye exam and psychosis symptom data were available. These 531 participants included n=45 individuals with one or more symptoms of psychosis (probands), n=24 unaffected co-twins of the probands, and n=462 controls (participants with no symptoms of psychosis). Demographic information for these participants is presented in Table 1. The study was approved by the ethics committees of the Royal Victorian Eye and Ear Hospital, the Royal Hobart Hospital, and the QIMR Berghofer Medical Research Institute, as well as the Australian Twin Registry, and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all of the participants or their legal guardians, with the participants' assent before examination.

## 2.2. Measures

**2.2.1. Psychosis Symptoms**—Participants reported on six lifetime symptoms of psychosis during either a computer-assisted telephone interview or an online survey using the same items (Gillespie et al., 2013). Symptoms were taken from the modified Composite International Diagnostic Interview (CIDI) (Kessler et al., 2005). Several studies of community samples have shown that CIDI-assessed psychosis symptoms correlate with demographic factors and psychiatric symptoms in expected ways (Scott et al., 2006; Scott et al., 2008; van Os et al., 2001; Varghese et al., 2011). In our sample, CIDI-assessed psychosis symptoms were associated with mental health problems ( $r=0.19$ ,  $p<.001$ ), assessed with the Somatic and Psychological Health Report (Hickie et al., 2001a; Hickie et al., 2001b), and smoking ( $F=4.19$ ,  $p=.040$ ), similar to other measures of psychotic experiences given in community-based samples (Kelleher and Cannon, 2011; Kelleher et al., 2012). Table 2 shows the prevalence of each psychosis symptom, and the prevalence of each symptom matched the prevalence in the larger study from which participants were drawn. Because of the rarity of some of the symptoms, we collapsed the responses into a single categorical variable reflecting the presence versus absence of symptoms.

**2.2.2. Retinal vessel diameter**—As previously described (Sun et al., 2009a; Sun et al., 2009c), all of the twins had 10° stereoscopic optic disc-centered photographs using a Nidek 3-Dx/F fundus camera (Nidek) after dilatation of the pupils with tropicamide 1% or cyclopentolate 1%. Photographs were digitalized, and retinal vascular diameter was measured with computer-assisted software (IVAN, University of Wisconsin, USA) according to a standardized protocol (Wong et al., 2004). Two trained graders, masked to participant characteristics, performed the vessel measurements on the optic disc-centered image for both eyes for all of the participants. The largest 6 arterioles and venules coursing through a zone between half to 1 disc diameter from the optic disc margin were measured. As in the Dunedin Study (Meier et al., 2013), estimates were summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), representing the average diameter of arterioles and venules of the eye, respectively, using a revised Knudtson-Parr-Hubbard formula (Knudtson et al., 2003). Intra-grader variation was assessed in 67 randomly selected retinal photographs. The intra-grader intraclass correlation coefficient was 0.95 for CRAE and 0.99 for CRVE. Inter-grader reliability was assessed in 52 randomly selected retinal images, and the interclass correlation coefficient was 0.93 for CRAE and 0.98 for CRVE. The correlation between CRVE and CRAE was 0.51 (Sun et al., 2009c). Mean CRAE and CRVE values for the  $n=531$  that we report on here were 163.88  $\mu\text{m}$  ( $SD=12.50$ ) and 249.69  $\mu\text{m}$  ( $SD=17.55$ ), respectively. These means match published means for the larger study from which participants were drawn (Sun et al., 2009c).

**2.2.3. Covariates**—Smoking status was included as a covariate, as smoking is associated with both wider venular diameter and psychosis symptoms (Degenhardt et al., 2001; Ikram et al., 2012; Kelleher and Cannon, 2011; Meier et al., 2014; Morgan et al., 2014; Sun et al., 2009b). Body mass index was considered as a covariate because higher body mass index is associated with wider venular diameter (Ikram et al., 2012; Sun et al., 2009b) and is seen in psychosis (Foley et al., 2013; Morgan et al., 2014). Smoking status and body mass index were each assessed at the time of the eye exam.

### 2.3. Statistical Analysis

We tested whether (a) probands had wider venules than controls and (b) unaffected co-twins had venular diameters intermediate between probands and controls. We also tested whether, as in the Dunedin Study (Meier et al., 2013), psychosis symptoms were unrelated to arteriolar diameter. Prior to analyses, we adjusted vessel diameter for the effects of age, sex, axial length, and sphericity, because vessel diameter varies depending on these factors (Sun et al., 2009b). Vessel diameter was then standardized ( $M=0$ ,  $SD=1$ ). To account for participants' familial relatedness (the non-independence of observations), robust standard errors were computed using the SURVEYREG procedure in SAS (SAS Institute, Inc., Cary, NC, USA). This procedure downwardly adjusts the degrees of freedom based on the number of twin pairs in the analysis, taking into account that information obtained about one twin is related to information obtained about the co-twin.

### 3. Results

Figure 1 shows mean venular diameter for controls, unaffected co-twins, and probands. Means were adjusted for age, sex, axial length, and sphericity and standardized. The standardized scores reflect effect sizes for how different each group is from the sample mean and from each other group. Effect sizes of 0.20, 0.50, and 0.80 reflect small, medium, and large effects, respectively (Cohen, 1992). Consistent with hypotheses, probands had wider venules ( $M=0.29$ ) than controls ( $M=-0.04$ ) ( $t=2.25$ ,  $p=.03$ ), and unaffected co-twins had venular diameters that were intermediate between probands and controls ( $M=0.13$ ; linear trend  $t=2.16$ ,  $p=.03$ ).

Figure 2 shows the distribution of venular diameter (adjusted for age, sex, axial length, and sphericity and standardized) in each group. This figure shows that the distribution was shifted to the right in probands and unaffected co-twins. That is, 62% of probands and 67% of unaffected co-twins had venular diameters that were wider than the sample mean ( $Z=0.00$ ), compared with 45% of controls. Results of a non-parametric test, which does not rely on outliers, showed that, compared with controls, a greater proportion of probands ( $\chi^2=4.61$ ,  $p=.03$ ) and unaffected co-twins ( $\chi^2=4.15$ ,  $p=.04$ ) had wider than average venules.

We repeated analyses, controlling for smoking status, as there was some indication that smoking, but not body mass index, was elevated among probands and unaffected co-twins (Table 1). Results were virtually unchanged after controlling for smoking status. Smoking-adjusted means for controls, unaffected co-twins, and probands were -0.03, 0.12, 0.27, respectively. The difference in venular diameter between probands and controls remained statistically significant ( $t=2.15$ ,  $p=.03$ ), and the linear trend demonstrating that unaffected co-twins had venular diameters intermediate between probands and controls also remained statistically significant ( $t=2.06$ ,  $p=.04$ ).

There were no differences in arteriolar diameter between probands ( $M=0.11$ ), unaffected co-twins ( $M=-0.02$ ), and controls ( $M=-0.01$ ), consistent with the previous report of no association between psychosis symptoms and arteriolar diameter (Meier et al., 2013).

## 4. Discussion

Here we demonstrate that adolescent and young adult twins with one or more symptoms of psychosis, and their unaffected co-twins, have wide retinal venules. Findings are consistent with the recent Dunedin Study report that adults with symptoms of psychosis and adults diagnosed with schizophrenia have wide retinal venules (Meier et al., 2013). Our findings advance knowledge in two main ways. First, they show that the novel Dunedin Study finding is reproducible; replication is recognized as the gold standard in biomarker research and is especially important given the poor track record of biomarker research in psychiatry. The current study was conducted by an almost entirely independent team of investigators using a different research design in a sample from another country, suggesting that the finding of wide venules in individuals with symptoms of psychosis may be robust. We know of no other attempts to replicate this very recent finding.

Second, our findings suggest that wide venules are related to familial liability to psychosis symptoms: A greater proportion of probands and unaffected co-twins had wider than average venules compared with controls, and unaffected co-twins had venular diameters that were intermediate between probands and controls. Thus, an intriguing possibility is that wide venules reflect susceptibility to psychosis symptoms as opposed to a consequence of psychosis symptoms. This finding bolsters the implication from the Dunedin Study that wide venules are associated with vulnerability to schizophrenia, as cohort children who exhibited symptoms of psychosis but did not develop schizophrenia had wider venules as adults (Malaspina, 2013; Meier et al., 2013).

An understanding of the mechanisms underlying wider venules might provide insight into the pathogenesis of psychosis symptoms. Genetic factors influence venular diameter (Fahy et al., 2011; Ikram et al., 2010; Xing et al., 2006), indicating that some people are genetically predisposed to having wider venules. Inflammation, endothelial dysfunction, and hypoxia have also been found to be associated with wider venules, in addition to traditional cardiovascular risks, including obesity, impaired fasting glucose, dyslipidemia, and smoking (De Jong et al., 2008; Ikram et al., 2012; Klein et al., 2006; Nguyen et al., 2010; Sun et al., 2009b; Wong et al., 2006a). All of these factors have been implicated in schizophrenia (Barnett et al., 2007; Israel et al., 2011; Kirkpatrick and Miller, 2013; Mitchell et al., 2013; Ryan et al., 2003; Schmidt-Kastner et al., 2012), and some of these factors occur at higher than expected rates in unaffected relatives of patients with schizophrenia (Lyons et al., 2002; Martinez-Gras et al., 2012; Mukherjee et al., 1989; Nunes et al., 2006; Spelman et al., 2007) and in individuals with symptoms of psychosis (Degenhardt et al., 2001; Foley et al., 2013; Kelleher and Cannon, 2011).

An interesting question is whether wide venules in individuals with symptoms of psychosis and their unaffected relatives simply reflect the cumulative effects of these risks, or whether wide venules might be causally related to psychosis symptoms. We showed that the association between wider venules and psychosis symptoms was independent of smoking and body mass index in this young and otherwise healthy sample. It is unlikely that blood pressure could explain the wide venules in the probands and unaffected co-twins, because higher blood pressure is most consistently associated with narrower arterioles (Ikram et al.,



2012; Sun et al., 2009b), and there was no evidence of narrower arterioles in probands or unaffected co-twins. Concerns about the confounding effects of other cardiovascular risks are alleviated somewhat by the youth and health of the sample, but subclinical levels of risks, such as inflammation (Khandaker et al., 2014), should still be considered. We note that whether or not wide venules are causally related to psychosis symptoms, they might be especially useful indicators of cardiovascular risk in otherwise healthy adolescents and young adults with symptoms of psychosis, as conventional cardiovascular risk factors are difficult to detect in these populations.

Another question is whether wider retinal venules are specific to individuals with psychosis symptoms. In the Dunedin Study, individuals diagnosed with schizophrenia had wider venules than medical and psychiatric (i.e., persistent depression) comparison groups (Meier et al., 2013). In our sample of young adult twins, depression and anxiety symptoms were unrelated to venular diameter (Meier et al., 2014). Thus, initial findings suggest that wider venules may be specific to individuals with symptoms of psychosis, but further investigation is warranted.

This study should be interpreted in the context of limitations. First, it is possible that our measure of psychosis symptoms may not have captured 'true' or severe psychotic experiences. However, it is now clear that subclinical psychotic symptoms are common in the general population (Scott et al., 2006; van Os et al., 2009), and subclinical and clinical psychotic experiences vary along a continuum (Linscott and van Os, 2013; van Os et al., 2009). Moreover, etiological factors appear to be similar across this continuum (Kelleher and Cannon, 2011; van Os et al., 2009). Second, because of the small number of twin pairs discordant for psychosis symptoms, we had to combine discordant MZ and DZ pairs, precluding us from determining whether shared genetic factors or shared environmental factors account for the wide venules in the unaffected co-twins. Future follow-ups of our twins may allow us to parse genetic and environmental influences or, complementarily, to test the association between polygenic risk for schizophrenia and retinal venular diameter.

This study has a number of implications. First, as wide retinal venules predict cardiovascular and cerebrovascular diseases (Cheung et al., 2013; McGeechan et al., 2009a; McGeechan et al., 2009b; Wong et al., 2006b; Yatsuya et al., 2010), our findings add to the growing evidence base suggesting that individuals with psychosis may have an underlying vulnerability to these diseases (Andreassen et al., 2013; Kohen, 2004; Ryan et al., 2003; Spelman et al., 2007). Early intervention to improve cardiovascular health in individuals with symptoms of psychosis may be warranted. Second, we detected this vulnerability fairly early in life, attesting to the potential utility of retinal imaging for identifying cardiovascular risk in young people with symptoms of psychosis. Retinal venular diameter might be considered for addition to cardiovascular risk prediction models for individuals with psychosis (Osborn et al., 2014). Third, research on retinal venular diameter may help to clarify the pathophysiology of psychosis symptoms. Wide retinal venules may represent an endophenotype for psychosis and schizophrenia (Gottesman and Gould, 2003); wide venules are heritable (Fahy et al., 2011; Sun et al., 2009c; Taarnhoj et al., 2006) and are apparent in individuals with symptoms of psychosis and their unaffected relatives, as well as in individuals with schizophrenia (Meier et al., 2013). Thus, genetic research on retinal venular

diameter could potentially aid in the discovery of variants associated with psychosis and schizophrenia (Glahn et al., 2014).

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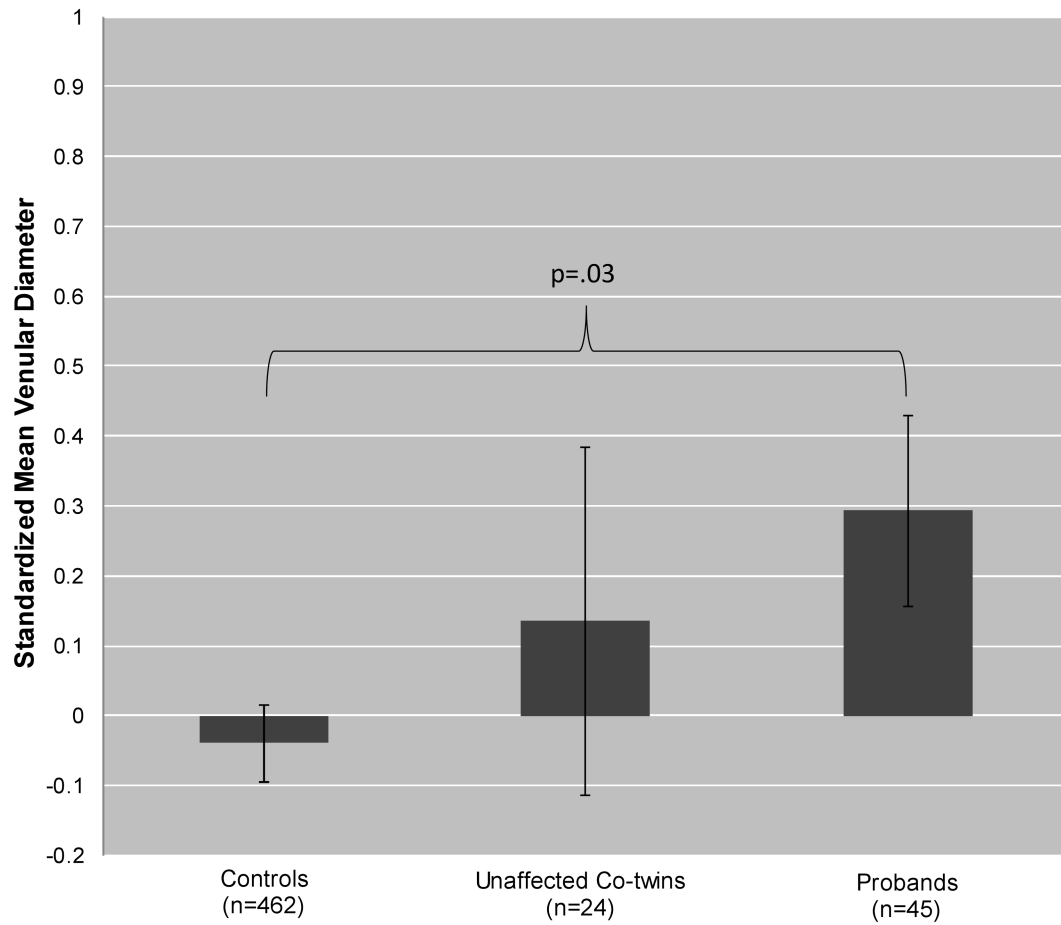


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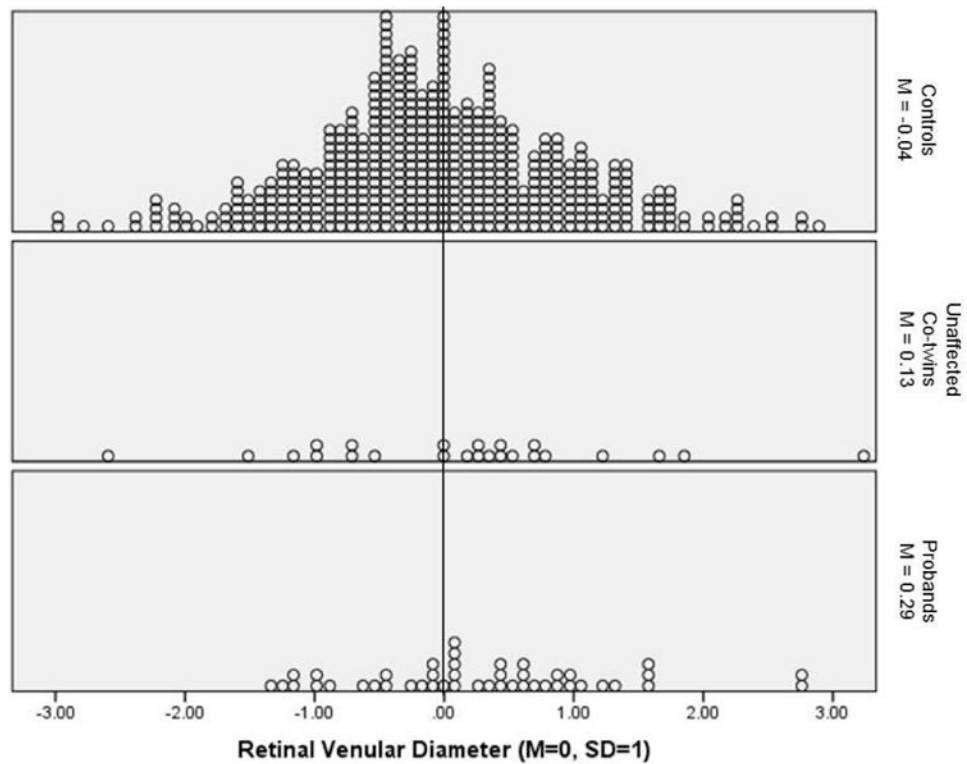
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**Figure 1.** Standardized Mean Venular Diameter for Controls, Unaffected Co-twins, and Probands. Error bars=robust standard errors. Means were adjusted for age, sex, axial length, and sphericity and standardized. These standardized means translate to units of micrometers ( $\mu\text{m}$ ) as follows: 248.99 (controls), 252.06 (unaffected co-twins), and 254.78 (probands).



**Figure 2.** Distribution of retinal venular diameter in controls, unaffected-cotwins, and probands. Venular diameter was adjusted for age, sex, axial length, and sphericity and then standardized to  $M=0$ ,  $SD=1$  in the full sample. The vertical line shows the sample mean of 0.00. A greater proportion of probands (62%) and unaffected co-twins (67%) had wider than average venules compared with controls (45%).



**Table 1**

Means (standard deviations) on demographic variables and health risks for controls, unaffected co-twins, and probands.

	Controls N=462	Unaffected Co-Twins N=24	Probands N=45
Sex (% Female)	61	58	58
Age at Eye Exam	20.74 (3.56)	19.67 (3.00)	19.91 (3.09)
Age at Psychosis Symptom Assessment	26.70 (3.53)	26.13 (3.59)	26.04 (3.27)
Smoker (%)	16	25	27
Body Mass Index	22.51 (3.63)	22.54 (4.06)	23.43 (4.55)

Note. All pairwise comparisons between groups were non-significant.

**Table 2**

Prevalence of psychosis symptoms among adolescents and young adults (n=531).

Symptom	N	%
Saw a vision that other people could not see.	26	5
Heard voices that other people could not hear.	19	4
Experienced mind control (thought insertion or extraction).	3	.6
Felt that mind was being taken over by strange forces.	3	.6
Experienced attempts at communication from strange forces.	5	1
Believed there was a plot to harm you.	5	1

Note. '0' symptoms: n=486; '1' symptom: n=33; 2+ symptoms: n=12. The prevalence of each psychosis symptom matched the prevalence in the larger study from which participants were drawn.

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