# The Prevalence and Significance of Anterior T wave Inversion in White, Young Athletes and Non-Athletes

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**ABSTRACT**

**Background:** Anterior T wave inversion (ATWI) on an EKG in young white adults raises the possibility of cardiomyopathy, specifically arrhythmogenic right ventricular cardiomyopathy (ARVC). While the 2010 European consensus recommendations for EKG interpretation in young athletes state that ATWI beyond V1 warrants further investigation, the prevalence and significance of ATWI has never been reported in a large white asymptomatic population.

**Objective**: This study investigated the prevalence and significance of ATWI in a large cohort of young, white adults including athletes.

**Methods:** 14,646 individuals aged 16-35 years were evaluated with a health questionnaire, physical examination and 12-lead EKG, including 4,720 (32%) females and 2,958 (20%) athletes. ATWI was defined as T wave inversion in $\geq 2$ contiguous anterior leads (V1-V4) and was investigated comprehensively to elucidate cardiac pathology.

**Results:** ATWI was detected in 338 (2.3%) individuals and was more common in females than males (4.3% vs. 1.4%; $p<0.0001$), and among athletes compared with non-athletes (3.5% vs 2.0%; $p<0.0001$). TWI was predominantly confined to leads V1-V2 (77%). Only 1.2% of females and 0.2% of males exhibited ATWI beyond V2. None of the individuals with ATWI fulfilled diagnostic criteria for ARVC after further evaluation. During a mean follow-up period of 23.1 ($\pm$12.2) months none of the individuals with ATWI experienced an adverse event.

**Conclusions:** Anterior T wave inversion confined to V1-V2 is a normal variant or physiological phenomenon in asymptomatic white individuals without a relevant family history. Conversely, ATWI beyond V2 is rare, particularly in males, and may warrant investigation. These results will have a significant impact on EKG interpretation in young white adults.

**Key words:** anterior T wave inversion; arrhythmogenic right ventricular cardiomyopathy; EKG screening; ethnicity

**Abbreviations:**
ARVC- arrhythmogenic right ventricular cardiomyopathy
ATWI- anterior T wave inversion
CMRI- cardiac magnetic resonance imaging
EKG- electrocardiogram
TWI- T wave inversion

**Introduction**

There is general agreement that T wave inversion (TWI) in the inferior or lateral leads in young individuals warrants further investigation for cardiac disease, particularly cardiomyopathy (1). It is also well-established that adolescent athletes (2-6) and black adult athletes (7) frequently exhibit TWI in the anterior leads as part of the normal physiological or ethnic spectrum respectively. However, the general consensus on the significance of anterior T wave inversion (ATWI), defined as T wave inversion in ≥2 contiguous anterior leads (V1-V4) in white adults varies between expert recommendations for the interpretation of the athlete's EKG. Whereas the European Society of Cardiology recommendations suggest further evaluation of athletes with TWI beyond V1 (8), more recent recommendations from the Seattle criteria advocate investigation only if TWI extends beyond V2 (9).

Both consensus panels have relied on data from unselected (10) or small athlete cohorts (11); however recent studies reveal that TWI in leads V1-V2/V3 is detected in up to 6% of endurance athletes (12). Conversely, ATWI in V1-V2/V3 is a recognized repolarization abnormality in a significant proportion of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and a small minority of patients with hypertrophic cardiomyopathy (7) which collectively account for > 40% of all sudden cardiac deaths (SCD) in young athletes (13). The differentiation of potentially pathological ATWI from a pattern that represents a normal variant or physiological remodelling in white adult athletes is essential to minimize the risk and consequences of an erroneous diagnosis (6,14).

Since the prevalence of ATWI has been reported in black athletes and controls of both sexes, and in the adolescent population, this study focused on the prevalence and significance of

87 ATWI in a large cohort of apparently healthy white adults including a large proportion of

88 athletes.

89 **Methods**

90 *Setting*

91      The UK does not support a nationally sponsored screening programme for cardiac disease

92 in young asymptomatic individuals in the absence of a family history of inherited cardiac disease

93 or premature SCD. Several elite sporting organizations finance the evaluation of their athletes

94 through the charitable organization, Cardiac Risk in the Young (CRY). These include premier

95 league football clubs, the Lawn Tennis Association and the English Institute of Sport. Up to

96 1000 athletes are tested annually at their specific clubs or national training camps, usually with

97 history, examination and EKG. Financially endowed organisations such as the Football

98 Association and the Lawn Tennis Association also incorporate echocardiography as standard.

99      CRY also offers cardiac screening to all young (14- 35 years old) individuals who wish to

100 be assessed even in the absence of symptoms, past history of cardiac disease or a family history

101 of inherited cardiac diseases or SCD. Such screenings are conducted at community centres and

102 high schools and are limited to history, examination and EKG with referral for further

103 assessment only in those with abnormal preliminary investigations or if participating as controls

104 for research studies. Screening events are advertised via the local media and on the CRY website

105 (www.c-r-y.org.uk). Individuals from the general population, including those from local high

106 schools, self-present to screening events whereas competitive athletes attend specified screening

107 events mandated by their relevant sporting bodies. The CRY screening program is supervised by

108 S.S. (principal investigator).

109 *Subjects*

Between 2007 and 2013, 14,646 young, white adults aged between 16 and 35 years, underwent cardiac evaluation through CRY at various testing centres in England. Ethnicity was self-reported through the questionnaire that included terms such as white British, white Irish, white European and white other.

*Athletes*

The study included 2958 (20.2%) athletes competing at regional, national or international level who performed ≥8 hours of exercise per week. Sporting disciplines were categorized as predominantly endurance or strength. Endurance sports were defined as those typically resulting in >70% of maximal oxygen uptake ($VO_{2\ max}$) (15) and included badminton, basketball, canoeing, cycling, hockey, middle and long-distance running, rowing, rugby, soccer, squash, swimming, tennis and triathlon. All other sports were deemed strength disciplines, including cricket, diving, sailing, volley ball, water polo, weight-lifting and wrestling.

*Non- Athletes*

Non-athletes comprised of 11,688 (79.8%) individuals, whose primary inclusion criterion was a sedentary lifestyle (≤ 2 hours organized physical activity per week). Individuals with symptoms suggestive of cardiac disease, previous cardiac history or a family history of premature cardiac disease or SCD (<50 years) were excluded.

*Investigations*

Electrocardiogram

A standard 12-lead EKG was performed in a supine position using a Marquette Hellige recorder (Milwaukee, USA) at a paper speed of 25 mm/s. P, Q, R, S, T wave voltages, ST segments, QRS, PR, and QT intervals were measured in each lead as described elsewhere (16). Leads V1-V4 were classified as anterior precordial leads. T wave deflection ≥ -0.1mV in these

133  leads was regarded as abnormal T wave inversion. Deep T wave inversion was defined as a T

134  wave amplitude ≥ -0.2mV. In cases of biphasic T waves we applied the above definition to the

135  negative component of the T wave. In cases with ATWI, the EKG was repeated ensuring that the

136  leads were correctly positioned according to standard recommendations. In women the EKG

137  electrodes were placed under the breast tissue as per American Heart Association

138  recommendations (17). Partial right bundle branch block (pRBBB) was defined as QRS duration

139  >0.1 but <0.12 seconds, with rSR' morphology in lead V1 and qRS in V6 (18). Individuals with

140  TWI and complete right bundle branch block (QRS ≥0.12 seconds) were excluded from the

141  ATWI group.  Additional EKG markers compatible with ARVC were also sought, including

142  terminal activation duration of the QRS complex ≥ 55msec in leads V1, V2 or V3, and the

143  epsilon wave (19).

144       The amplitude of the J-point (Jt) (20) was measured at the end of the QRS complex (the

145  onset of the ST segment) with reference to the onset of the QRS complex. The Jt was considered

146  elevated if Jt ≥0.1mV or depressed if Jt ≤ -0.1mV. The morphology of the ST segment in the

147  anterior leads was ascertained in the M interval (the 100ms following Jt) (20). Accordingly, the

148  ST segment at the onset of the M interval, i.e. Jt, was considered elevated if it were above Jt,

149  depressed if it were below Jt and isoelectric if it were in line with Jt. Ascending ST segments

150  were categorised as ascending convex or ascending concave (figure 1).

151  Echocardiogram

152       Two-dimensional (2D) transthoracic echocardiography was performed on all subjects

153  with ATWI, with Philips (CPX50, iE33, Sonos 7500) and GE Vivid I (Tiral, Israel) machines.

154  Standard views were obtained and dimensions of cavities and wall thickness measurements,

155  pulsed colour and tissue Doppler measurements were made in accordance with established

156  guidelines (21-23) Right ventricular (RV) assessment was performed as outlined previously (14).

157  RV regional wall-motion abnormalities (WMAs) were defined as akinetic, dyskinetic, or

158  aneurysmal, in accordance with diagnostic criteria for ARVC (19).

159      Echocardiography was also performed as standard on 1079 athletes and 769 non-athletes

160  without ATWI of similar age and sex proportion who had normal physical examination and

161  EKG. The echocardiogram was part of a mandatory pre-participation cardiac evaluation in

162  athletes whereas the echocardiogram was conducted as part of research in volunteering non-

163  athletes. These cohorts served as comparative groups for athletes and non-athletes with ATWI

164  respectively.

165      All EKG and echocardiograms were performed by nationally-accredited cardiac

166  physiologists. Echocardiography was conducted by physiologists blinded to the EKG findings.

167  All EKG and echocardiogram images were reviewed by 2 independent cardiologists with the

168  principal investigator (S.S.) adjudicating any queries.

169  *Further Investigations*

170      All subjects with ATWI underwent additional investigations to detect the broader

171  phenotypic features of a primary cardiomyopathy, particularly ARVC, hypertrophic

172  cardiomyopathy and dilated cardiomyopathy. Pre-determined diagnostic criteria for ARVC were

173  based on the 2010 Modified Task Force criteria (19). Hypertrophic cardiomyopathy was

174  considered in individuals with left ventricular hypertrophy where septal or wall thickness

175  measured ≥15mm in any myocardial segment in the absence of another condition capable of

176  producing left ventricular hypertrophy of the same magnitude (24,25). Dilated cardiomyopathy

177  was considered in individuals with a dilated LV (males >59mm and females >53mm) when

178    accompanied by a reduced ejection fraction (< 52%) (29). The vast majority (1396; 95%) of

179    further investigations were performed at our institution.

180    <u>Ambulatory EKG monitoring</u>

181        Ambulatory 24-hour EKG recording (Lifecard CF Holters, Spacelabs Healthcare, USA)

182    was used to detect ventricular arrhythmias. Subjects were encouraged to continue day-to-day

183    activities including exercise during monitoring.

184    <u>Exercise-testing</u>

185        Exercise testing was performed upright on a treadmill using the standard Bruce protocol

186    (27). Subjects were exercised to volitional exhaustion and assessed for cardiac symptoms,

187    ischaemic changes, attenuated blood pressure response or arrhythmias.

188    <u>Signal-averaged EKG</u>

189        Signal-averaged EKG was acquired according to accepted methodology using the same

190    machines used for standard electrocardiography, with use of a 40Hz high-pass bi-directional

191    filter (28). Late potentials were defined as abnormal values in one or more of the parameters in

192    accordance the diagnostic criteria for ARVC (19).

193    <u>Cardiac Magnetic Resonance Imaging</u>

194        CMRI was performed using a Philips Achiever 3.0T TX scanner (Amsterdam, the

195    Netherlands). Delayed gadolinium enhancement (DGE) images were acquired as previously

196    described (29). Ventricular volumes and function were measured for both ventricles using

197    standard techniques and analysed using semi-automated software (Extended MR workspace,

198    Philips, Amsterdam, the Netherlands) (30). All measures were indexed to body surface area.

199    *Ethical approval*

200   Ethics approval was granted by the National Research Ethics Service, Essex 2 Research

201   Ethics Committee in the United Kingdom. Written consent was obtained from all subjects.

202   *Statistical analysis*

203   Data are expressed as mean (±SD) or percentages as appropriate and analyzed with SPSS

204   software, version 20 (Chicago, IL). Comparison between groups was performed using Student t-

205   test for continuous variables with adjustment for unequal variance if needed and $\chi^2$ tests or Fisher

206   Exact Tests for categorical variables. Univariate analyses were performed to determine variables

207   (gender, age, athletic status, left ventricular end diastolic diameter and right ventricular outflow

208   tract size (parasternal long and short axis measurements)) associated with ATWI. Multivariate

209   logistic regression analyses were used to determine the independence of these associations.

210   Significance was defined as $p<0.05$.

211   **Results**

212   *Demographics*

213   The mean age of the cohort was 21.7 (±5.4) years.  Of the 14,646 subjects, 9,926 (67.8%)

214   were male. 2063 (20.8%) males and 895 (19.0%) females were athletes. Athletes exercised for an

215   average of 15.7 (±5.1) hours/ week compared with 1.8 (±0.6) hours/ week in non-athletes.

216   Prevalence of Anterior T wave Inversion

217   338 individuals (2.3%) exhibited ATWI. Individuals with ATWI were of similar age and

218   had a similar mean body surface area compared to those without ATWI (**Table 1**). Anterior T

219   wave inversion was more common in females compared with males (n= 203; 4.3% vs n= 135;

220   1.4%: p<0.0001) and was more common in athletes than non-athletes (n= 103; 3.5% vs. n= 235;

221   2%; p<0.0001) in both sexes (females: n= 58; 6.5% vs. n= 145; 3.8%; p= 0.0005, and males: n=

222   45; 2.1% vs. n= 90; 1.1%; p= 0.0004) (**Central Illustration**). Among athletes, ATWI was more

223  prevalent in those engaging in endurance sports compared to strength sports (n= 82; 5.6% vs.

224  n=41; 2.8%: p<0.0001). The prevalence of ATWI among those aged 16-21 years was not

225  dissimilar to those aged above 21 years (2.28% vs 2.46%; p= 0.52).

226  <u>Distribution of Anterior T wave Inversion</u>

227  260 individuals (1.8%) revealed TWI confined to V1-V2. TWI confined to V1-V2

228  constituted 77% of all ATWI. Only 78 (0.5%) individuals demonstrated TWI beyond V2 which

229  was present in 56 (1.2%) females vs. 22 (0.2%) males (p<0.0001). Among athletes, TWI in V1-

230  V3 was detected in 19 (2.1%) females vs. 7 (0.3%) males (p<0.0001) (figure- central

231  illustration). Four females, but none of the males, showed TWI extending to V4, which equated

232  to just 2% of all ATWI in females.

233  Deep ATWI was more common in males than females (55.6% vs. 33%; p=0.0166) but

234  did not differ between athletes and non-athletes. 50 individuals with ATWI (14.8%) exhibited

235  incomplete RBBB which never extended beyond V2.

236  <u>Jt elevation and ST segment morphology preceding ATWI</u>

237  Among individuals with ATWI, Jt elevation was more common in athletes than non-

238  athletes (49% vs. 29%; p=0.0008) and more common in males than females irrespective of

239  athletic status (athletes: 71.1% vs. 31.0%, p= 0.0004; non-athletes: 58.9% vs. 10.3%, p< 0.0001).

240  None of the individuals with ATWI demonstrated a depressed Jt.

241  Males frequently showed an elevated ST-segment that of ascending convex morphology

242  (42%), followed by an ascending concave morphology (33%) and an isoelectric pattern (25%).

243  In females with ATWI the ST segment was most commonly isoelectric (57%), followed by

244  ascending convex (24%) and ascending concave (19%) morphologies. Only one individual with

245  ATWI demonstrated a depressed ST segment (**Figure 2**).

246     Cardiac Structure and Function in Individuals with ATWI

247        The echocardiographic results of all 338 individuals with ATWI (athletes= 103, non-

248   athletes= 235) were compared with the results of 1848 individuals without ATWI (athletes=

249   1079, non-athletes= 769). Athletes revealed larger ventricular dimensions compared to non-

250   athletes irrespective of ATWI. There were no differences in left or right ventricular dimensions

251   or function in individuals (athletes and non-athletes) with ATWI compared to those without

252   AWTI (**Table 2**).

253        CMRI was performed on 250 (74%) subjects with ATWI. Athletes demonstrated larger

254   left and right ventricular volumes and masses compared to non-athletes (**Table 2**). Following

255   gadolinium there was no evidence of late enhancement in any subject. None of the individuals

256   with ATWI showed unequivocal diagnostic features of ARVC, hypertrophic cardiomyopathy or

257   dilated cardiomyopathy.

258   *Other Investigations*

259   Signal-averaged Electrocardiogram

260        316 (93%) individuals with ATWI underwent SAEKG and 21 (7%) showed an

261   abnormality in one of the three parameters. The most common abnormality was filtered QRS

262   prolongation (60%), a phenomenon that has been reported previously in healthy individuals

263   (31,32).

264   Exercise Stress Testing and Ambulatory EKG Monitoring

265        274 (81%) individuals with ATWI underwent an exercise stress test and 293 (87%) had

266   24 hour EKG monitoring. None of the individuals with ATWI exhibited an arrhythmia during

267   exercise, other than occasional isolated ventricular ectopics (n= 10; 3%) of right or left

268   ventricular origin in the early stages of exercise. Similarly, none showed >500 ventricular

269   ectopics or runs of non-sustained ventricular tachycardia during Holter monitoring (19).

270   Determinants of Anterior T wave Inversion

271   Univariate predictors of ATWI were female gender and athletic status. Stepwise logistic

272   regression identified female gender (OR 3.1, 95% CI 1.96-4.90, p<0.001) and athletic status (OR

273   3.3, 95% CI 1.91-5.63, p=0.001) as being independently associated with ATWI in the screened

274   adult population, irrespective of age.

275   Detection of Cardiac Pathology

276   Following comprehensive clinical evaluation of 274 (81%) individuals with ATWI

277   (including echocardiography in all 338 individuals) and a mean follow-up period of 23.1 ±12.2)

278   months, we could not diagnose ARVC or any other cardiomyopathy. However, 16 athletes and

279   10 non-athletes with ATWI fell into the gray zone, in which structural changes attributed to

280   physiological adaptation needed to be differentiated from primary cardiomyopathies. These

281   included: 2 athletes and 3 non-athletes with an indexed $RVOT_{plax} \geq 19$ mm/m$^2$; 1 athlete with a

282   maximal left ventricular wall thickness of 13mm; and 6 non-athletes who initially demonstrated

283   an absolute LVEDD above the upper limit of normal (non-athletes: LVEDD; males >59mm and

284   females >53mm[26] and athletes with an LVEDD > 60mm[33]).

285   Identification of Minor Cardiac Pathology

286   Echocardiography in all 338 subjects with ATWI failed to show akinetic segments or

287   regional wall motion abnormalities affecting the right ventricle. A small proportion revealed

288   minor pathology in 5 (1.5%) including: bicuspid aortic valve (n= 2; 0.6%), mitral valve prolapse

289   with moderate mitral regurgitation (n= 1; 0.3%); atrial septal defect (n=1; 0.3%) and patent

290 ductus arteriosus (n= 1; 0.3%). 7 (2%) individuals had a patent foramen ovale noted and pectus

291 excavatum was noted in 2 (0.6%) cases.

292 **Discussion**

293       The detection of lateral or infero-lateral T wave inversion in young black or white

294 individuals has a relatively high yield for the diagnosis of cardiomyopathy (1). Whereas ATWI is

295 a benign variant in healthy adolescents of all ethnic origins and in black adolescent and adult

296 athletes, its significance in asymptomatic white adults is unknown. However, between 50-60% of

297 probands with ARVC show ATWI in leads V1-V3 (34). This study of almost 15,000 healthy,

298 white adults, including 4,720 females and almost 3,000 athletes, showed that ATWI beyond V1

299 was present in a small proportion of individuals (2.3%) and this prevalence fell to just 0.5%

300 beyond V2. ATWI was more common in females than males irrespective of athletic status and

301 validates data from much smaller studies from 6- 7 decades ago (35,36). Several postulations for

302 this gender difference have been proposed including varying levels of sympathetic innervation

303 and anatomical differences in chest wall structure, specifically breast tissue. Based on the fact

304 that the prevalence of anterior T wave inversion is almost identical in prepubertal males and

305 females (3) we suspect that sex differences in adults are likely to reflect differences in lead

306 placement as a result of increased breast tissue in females.

307 Prevalence of Anterior T wave Inversion in Athletes

308       Athletes demonstrated a greater prevalence of ATWI than non-athletes, particularly those

309 engaging in >15 hours/ week of exercise. Such intense exercise regimes, particularly in

310 endurance sports, place a greater haemodynamic load on the right ventricle that may manifest on

311 the EKG as ATWI. Our study however, was unable to demonstrate any structural differences in

312 the right ventricle between individuals with ATWI and those without.

Significance of Extrapolating Data from Probands with Cardiomyopathy to low-risk Populations

314        There are justifiable concerns about the association of ATWI with an underlying

315   cardiomyopathy such as ARVC or hypertrophic cardiomyopathy. While isolated ATWI is rare in

316   hypertrophic cardiomyopathy is a rare finding (2), ATWI beyond V2 in probands with ARVC is

317   common and classified as a major repolarization abnormality in the Revised Task Force Criteria

318   for ARVC (19). In this study, none of the athletes with ATWI in V2/V3 fulfilled diagnostic

319   criteria for ARVC based on a combination of health questionnaire, EKG, and echocardiography

320   in 100% of cases, SAEKG in 93%, 24 hour EKG in 87%, exercise testing in 81% and CMRI in

321   74% . This observation highlights that data derived from probands with ARVC for generating

322   diagnostic criteria lack specificity in low risk populations (29). However, TWI beyond V2 was

323   present in just 1 in 200 white adult athletes and could justify detailed assessment to exclude

324   ARVC or any other cardiomyopathy. Our data supports the consensus based Seattle

325   recommendations, which pragmatically suggest that only TWI beyond V2 in asymptomatic white

326   athletes requires further evaluation (9). However, these recommendations are at odds with the

327   European Society of Cardiology recommendations and the recently published refined criteria

328   (8,37). Given the potentially sinister ramifications of false negative tests with regard to ARVC in

329   particular more robust data is necessary before such criteria can be adopted with more certainly

330   in future updates for EKG interpretation in athletes.  This comprehensive study of a large

331   population of athletes with ATWI provides support for the Seattle consensus.

332   Potential Markers of Disease in Individuals with Anterior T wave Inversion

333        In athletes with TWI beyond V1, information from the preceding Jt or ST segment may

334   provide valuable diagnostic information when considering ARVC. Based on comparisons

335   between 45 athletes with ATWI and 35 patients with ARVC we have previously reported that a

336  Jt and ST segment in line with the onset of the QRS complex  or a depressed ST segment

337  preceding ATWI is a powerful discriminator between the two entities (29). Moreover, a recent

338  study examining ATWI as a marker of cardiomyopathy in a small cohort of athletes of black and

339  white ethnicity, showed that Jt elevation ($\geq$ 0.1mV) preceding the TWI excluded ARVC.[34] Our

340  large study of almost 15,000 white individuals provides validation for these concepts in males

341  but reveals that Jt may be in line with the onset of the QRS complex  in as many as 50% of

342  healthy females with ATWI. Importantly, only 1 athlete demonstrated ATWI with preceding ST

343  segment depression and none of the individuals with ATWI showed Jt depression suggesting that

344  the presence of such electrical markers may be pointers for cardiac pathology.

345      There remains the possibility that ATWI confined to V1-V2 may be a manifestation of

346  ARVC. We have examined our own cohort of 35 probands with ARVC and identified ATWI in

347  V1-V2 alone in 6%. All of these patients either expressed symptoms or other electrical features

348  diagnostic of ARVC (29).

349  **Limitations**

350      This study was cross-sectional in nature and although there were no adverse clinical

351  events in the ATWI group during a follow-up of nearly 2 years, the authors cannot be certain

352  whether ATWI may precede the development of ARVC by several years. Familial evaluation

353  was not performed in any of the individuals with ATWI because none fulfilled overt criteria for a

354  cardiomyopathy. However, the authors concede that such practice may have highlighted some

355  individuals with incomplete expression of disease.  A small proportion of ATWI individuals

356  were lost to follow up due to logistical difficulties that could not be overcome (e.g. emigration).

357  Cardiac MRI is the recognized gold standard for the investigation of primary cardiomyopathies

358  but was only performed in 250 (74%) individuals with ATWI. However, 81% of all individuals

359 with ATWI had all of EKG, echocardiography, SAEKG, Holter and exercise stress test which

360 are sufficient to diagnose ARVC according to modified task force criteria (19). Voluntary

361 cardiac screening programmes of non-athletes in the community conducted through

362 organizations such as CRY do have a potential for inherent selection bias though given the large

363 numbers included in this study of nearly 15,000 participants, the potential of any such bias is

364 significantly mitigated.

365 **Conclusions**

366 ATWI is present in 2.3% of the young white population and is more common in females

367 and in athletes. Almost 80% is confined to V1-V2 and has a poor diagnostic yield for cardiac

368 pathology, implying that this electrocardiographic pattern could be considered a normal

369 phenomenon in asymptomatic individuals without a family history of cardiomyopathy or

370 premature SCD. In contrast, TWI extending beyond V2 is present in only 1% females and 0.2%

371 males and may justify further evaluation in white individuals, particularly when preceded by Jt

372 depression or ST segment depression.

373

374 **Clinical Perspectives**

375 Competency in Medical Knowledge: Anterior T wave inversion confined to V1-V2 may be a

376 normal variant or physiological phenomenon in asymptomatic white individuals without a

377 relevant family history.

378 Translational Outlook: The results of this study will have a significant impact on EKG

379 interpretation in young white athletes and non-athletes as the rarity of T wave inversion beyond

380 V2 (1 in 200) may justify further investigation.

381

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480

481    **Figure Legends**

482    **Central illustration: Prevalence of anterior T wave inversion (ATWI) in the adult white**

483    **population aged 16-35 years old.** The overall prevalence of ATWI in adult white individuals

484    was 2.3%. ATWI was more common in females and in athletes. The prevalence of ATWI

485    beyond V2 was rare, falling to 0.2% in male non-athletes.

486    **Figure 1: ST segment morphology**.(A) The vertical solid line and the vertical dashed line

487    define the M interval, which has a duration of 100ms. The horizontal dashed line through the

488    onset of the QRS complex provides the reference point for the measurement of Jt. Jt is elevated

489    at 0.2mV with a convex appearance.  ST segment morphologies with anterior T wave inversion

490    in chest leads V2 and V3 are shown as: B) ascending convex; C) isoelectric; D) ascending

491    concave; E) depressed.

492    **Figure 2: Bar graph demonstrating the type of ST segment morphology preceding anterior**

493    **T wave inversion (ATWI) in healthy individuals and ATWI according to sex.** An ascending

494    convex and ascending concave ST segment morphology was more common in males than

495    females.  Females more commonly demonstrated an isoelectric ST segment.

496

497 **Table 1: Demographics and EKG characteristics of individuals with and without anterior**

498 **T wave inversion**

| | Characteristic | Anterior TWI population (n =338) | Population without anterior TWI (n=14,308) | p value |
|---|---|---|---|---|
| **Demographics** | Age (years) | 21.1 ± 5.4 | 21.7 ± 5.3 | 0.0398 |
| | Sex (% female) | 60.1 | 31.6 | <0.0001 |
| | Athletes (%) | 30.5 | 20.0 | 0.0003 |
| | BSA (m$^2$) | 1.81 ± 0.3 | 1.91 ± 0.2 | <0.0001 |
| | Blood pressure (mmHg) | 121/66 ±12/7 | 123/80 ±10/6 | 0.0003 |
| | | | | |
| **EKG parameters** | Heart rate (bpm) | 64 ± 14 | 66 ± 14 | <0.0001 |
| | PR (ms) | 150 ± 25 | 151 ± 32 | <0.0001 |
| | QRS (ms) | 93 ± 12 | 92 ± 13 | <0.0001 |
| | QTc (ms) | 421 ± 28 | 412 ± 20 | <0.0001 |
| | Incomplete RBBB (%) | 17.7 | 5.5 | <0.0001 |
| | LBBB (%) | 0 | 0.02 | 0.77 |
| | LVH (%) | 17.9 | 10.1 | <0.0001 |
| | RVH (%) | 1.2 | 1.1 | 0.93 |
| | ER (%) | 15.1 | 9.7 | 0.0018 |
| | Pathol Q waves (%) | 0.5 | 0.3 | <0.0001 |
| | LA enlargement (%) | 3.3 | 1.4 | 0.002 |
| | RA enlargement (%) | 1.4 | 0.6 | 0.1 |

| | | | |
|---|---|---|---|
| LAD (%) | 1.0 | 1.2 | 0.83 |
| RAD (%) | 0.7 | 0.4 | 0.49 |
| Pre-excitation (%) | 0.5 | 0.5 | 0.93 |

499

500

501    Values are mean ± SD or % overall population

502    BSA= body surface area; EKG = 12 lead electrocardiogram; ER = early repolarisation; LA = left

503    atrial; LAD = left axis deviation; LBBB= left bundle branch block; LVH= left ventricular

504    hypertrophy; RA = right atrial; RAD = right axis deviation; RVH = right ventricular hypertrophy;

505    TWI = T wave inversion.

**Table 2: Echocardiographic and Cardiac Magnetic Resonance Measurements of Athletes and Non-athletes with and without Anterior T wave Inversion.**

| Measurement | Athletes (n= 1182) | | | Non-athletes (n= 1,004) | | |
|---|---|---|---|---|---|---|
| | With Ant TWI ( n= 103) | Without Ant TWI (n= 1079) | p value | With Ant TWI (n=235) | Without Ant TWI (n= 769) | p value |
| Ao (mm) | $28.0 \pm 4.3$ | $28.6 \pm 4.5$ | 0.2306 | $27.1 \pm 3.6$ | $27.4 \pm 3.8$ | 0.2839 |
| LA (mm) | $33.1 \pm 6.1$ | $33.5 \pm 4.9$ | 0.4394 | $31 \pm 4.3$ | $31.3 \pm 5.5$ | 0.443 |
| LVEDd (mm) | $50.8 \pm 5.8$ | $51.5 \pm 5.6$ | 0.2272 | $48.1 \pm 4.5$ | $48.5 \pm 5.8$ | 0.3315 |
| LVESd (mm) | $34.0 \pm 6.1$ | $33.9 \pm 4.8$ | 0.844 | $31.1 \pm 3.9$ | $31.6 \pm 5.1$ | 0.1666 |
| MLVWT (mm) | $9.2 \pm 2.3$ | $8.9 \pm 2.1$ | 0.1699 | $8.5 \pm 2.2$ | $8.3 \pm 1.5$ | 0.1126 |
| LVMI (g/m$^2$) | $105 \pm 15$ | $103 \pm 16$ | 0.2233 | $94 \pm 8$ | $95 \pm 9$ | 0.1267 |
| EF (%) | $60 \pm 9$ | $59 \pm 8$ | 0.231 | $66 \pm 8$ | $67 \pm 9$ | 0.1267 |
| RVOT$_{plax}$ (mm) | $29.9 \pm 5.4$ | $29.8 \pm 4.8$ | 0.8417 | $26.0 \pm 3.7$ | $25.4 \pm 3.6$ | 0.1072 |
| RVOT$_{plax}$ in$_{(mm/m^2)}$ | $16.7 \pm 2.1$ | $16.8 \pm 3.7$ | 0.7871 | $15.2 \pm 2.5$ | $14.8 \pm 3.1$ | 0.2041 |
| RVOT$_{psax}$ (mm) | $31.6 \pm 4.9$ | $32.3 \pm 5.6$ | 0.221 | $28.2 \pm 5.8$ | $29.1 \pm 5.7$ | 0.1266 |
| RVOT$_{psax}$in$_{(mm/m^2)}$ | $17.8 \pm 2.5$ | $17.5 \pm 2.9$ | 0.3106 | $16.0 \pm 2.1$ | $16.1 \pm 2.5$ | 0.6945 |
| RVOT2 (mm) | $25.8 \pm 4.8$ | $25.1 \pm 4.4$ | 0.1263 | $22.6 \pm 3.7$ | $23.2 \pm 4.3$ | 0.0537 |

| | | | | | | |
|---|---|---|---|---|---|---|
| RVD1 (mm) | 41.1 ± 6.6 | 40.6 ± 5.8 | 0.4093 | 35.3 ± 4.9 | 35.6 ± 5.5 | 0.4534 |
| RVD2 (mm) | 34.1 ± 6.4 | 33.3 ± 5.5 | 0.165 | 28.2 ± 4.5 | 28.7 ± 5.7 | 0.2181 |
| RVD3 (mm) | 84.2 ± 10.5 | 82.0 ± 13.2 | 0.1008 | 73.5 ± 11.4 | 74.9 ± 11.1 | 0.093 |
| RVWT (mm) | 4.8 ± 1.5 | 4.6 ± 1.3 | 0.1416 | 4.2 ± 0.8 | 4.1 ± 1.0 | 0.1613 |
| TAPSE (mm) | 23.4 ± 5.3 | 23.5 ± 4.2 | 0.8219 | 22.8 ± 4.7 | 22.9 ± 4.5 | 0.768 |
| PASP (mmHg) | 17.6 ± 7.7 | 15.9 ± 6.5 | 0.0128 | 17.8 ± 3.3 | 18.3 ± 4.0 | 0.0816 |
| TV E/A | 1.9 ± 0.5 | 2.0 ± 0.4 | 0.0181 | 1.9 ± 0.6 | 2.0 ± 0.8 | 0.0771 |
| TV S' (cm/s) | 14.8 ± 2.6 | 14.9 ± 2.5 | 0.6992 | 14.6 ± 2.8 | 14.2 ± 2.8 | 0.0556 |
| TV E' (cm/s) | 13.9 ± 3.4 | 14.1 ± 3.1 | 0.5353 | 14.9 ± 2.9 | 15.1 ± 3.5 | 0.426 |
| RAA (cm$^2$) | 19.2 ± 3.4 | 18.8 ± 3.7 | 0.2915 | 15.2 ± 2.8 | 15.1 ± 4.8 | 0.7613 |
| RV FAC (%) | 38.7 ± 4.9 | 39.6 ± 4.8 | 0.0698 | 36.2 ± 4.1 | 37.3 ± 6.2 | 0.0108 |

| CMR | ATWI Athletes (n=76) | | ATWI Non-athletes (n=174) | |
|---|---|---|---|---|
| LVM- i (g/m$^2$) | 105 ± 15 | | 94 ± 9 | $p < 0.05$ |
| LVEDV- i (ml/m$^2$) | 105.8 ± 15 | | 94.3 ± 14 | $p < 0.05$ |
| RV EF (%) | 52.5 ± 5.1 | | 55.5 ± 5.9 | $p < 0.05$ |
| RVEDV- i (ml/m$^2$) | 105.3 ± 14 | | 94.3 ± 14 | $p < 0.05$ |

| LGE (%) | 0 | 0 | - |

Values are mean ±SD. Ao= aorta; CMR= cardiac magnetic resonance imaging; EF= ejection fraction by Simpson's biplane; LA= left atrial; LVEDd= left ventricular end diastolic diameter; LVEDV= left ventricular end diastolic volume; LVESd= left ventricular end systolic diameter; LVM i = left ventricular mass index ($g/m^2$); MLVWT= maximum left ventricular wall thickness; PASP= pulmonary artery systolic pressure; RAA= right atrial area; RVD1= right ventricular basal dimension; RVD2= right ventricular midventricular dimension; RVD3= right ventricular longitudinal dimension; RVEDV= right ventricular end diastolic volume; RV `EF= right ventricular ejection fraction; RVOT1= proximal right ventricular outflow tract dimension; RVOT2= distal right ventricular outflow tract dimension; RVOTplax= right ventricular outflow tract dimension (parasternal); ; RVOTsax= right ventricular outflow tract dimension (short axis); RVWT= right ventricular free wall thickness; S'= peak systolic velocity; TAPSE= tricuspid annular plane systolic excursion; TV= tricuspid valve.