

SUPPLEMENTAL MATERIAL

| Supplemental table 1A: Generalized linear mixed model of the conduction times | | | | | | | | | | | | |
|--|----------------------|----------------|---------|------------------|-----------------|---------|-------------------|-----------------|---------|------------|-----------------|---------|
| | P-wave duration (ms) | | | PR-interval (ms) | | | QRS-duration (ms) | | | QTc (ms) | | |
| Model 1 (age, Type and Sex separated) | | | | | | | | | | | | |
| Fixed effects | β (95% CI) | | p value | β (95% CI) | | p value | β (95% CI) | | p value | β (95% CI) | | p value |
| Age | 0.28 | 0.25 – 0.31 | <0.001 | 0.38 | 0.32 – 0.43 | <0.001 | 0.05 | 0.02 – 0.09 | 0.001 | 0.54 | 0.49 – 0.60 | <0.001 |
| Type (FD patient) | 1.40 | 0.02 – 2.77 | 0.046 | -14.65 | -18.00 – -11.30 | <0.001 | 2.92 | 1.35 – 4.48 | <0.001 | -1.18 | -3.82 – 1.46 | 0.381 |
| Sex (Male) | 6.94 | 6.21 – 7.67 | <0.001 | 8.54 | 7.09 – 9.99 | <0.001 | 9.93 | 9.23 – 10.62 | <0.001 | -8.84 | -10.33 – -7.36 | <0.001 |
| Model 2 (Controls and FD patients combined groups- with age*Type*Sex interactions) | | | | | | | | | | | | |
| (Intercept) | 96.62 | 95.00 – 98.23 | | 140.30 | 136.94 – 143.66 | | 90.91 | 89.30 – 92.53 | | 401.60 | 398.23 – 404.97 | |
| Age | 0.26 | 0.22 – 0.29 | <0.001 | 0.33 | 0.26 – 0.40 | <0.001 | 0.03 | -0.01 – 0.07 | 0.114 | 0.44 | 0.37 – 0.51 | <0.001 |
| Type (FD patient) | -7.40 | -12.02 – -2.77 | 0.002 | -43.83 | -55.51 – -32.14 | <0.001 | -34.51 | -39.91 – -29.12 | <0.001 | -38.99 | -49.24 – -28.74 | <0.001 |
| Sex (Male) | 4.55 | 1.95 – 7.15 | 0.001 | 7.10 | 1.75 – 12.46 | 0.009 | 13.27 | 10.70 – 15.83 | <0.001 | -9.09 | -14.48 – -3.70 | 0.001 |
| Interactions | | | | | | | | | | | | |
| Age*Type (FD patient) | 0.24 | 0.14 – 0.34 | <0.001 | 0.71 | 0.45 – 0.97 | <0.001 | 0.90 | 0.77 – 1.02 | <0.001 | 0.82 | 0.60 – 1.05 | <0.001 |
| Age*Sex (Male) | 0.06 | 0.00 – 0.11 | 0.045 | 0.03 | -0.09 – 0.14 | 0.653 | -0.09 | -0.15 – -0.03 | 0.002 | -0.01 | -0.12 – 0.11 | 0.904 |
| Type (FD patient)*Sex (Male) | 11.44 | 4.29 – 18.59 | 0.002 | 39.40 | 21.08 – 57.71 | <0.001 | 0.89 | -7.56 – 9.34 | 0.837 | -20.13 | -36.05 – -4.20 | 0.013 |
| Age*Type (FD patient)*Sex (Male) | -0.26 | -0.43 – -0.10 | 0.002 | -0.84 | -1.27 – -0.42 | <0.001 | 0.21 | 0.00 – 0.42 | 0.049 | 0.82 | 0.46 – 1.19 | <0.001 |

| Supplemental table 1B: Generalized linear mixed model of the other LV related ECG parameters | | | | | | | | | |
|--|--------------------|---------------|---------|-------------------------|-----------------|---------|----------------------|----------------|---------|
| | Cornell index (mm) | | | Spatial QRS-T angle (°) | | | Frontal QRS-axis (°) | | |
| <i>Model 1 (age, Type and Sex separated)</i> | | | | | | | | | |
| Fixed effects | β (95% CI) | | p value | β (95% CI) | | p value | β (95% CI) | | p value |
| Age | 0.04 | 0.02 – 0.05 | <0.001 | 0.53 | 0.47 – 0.60 | <0.001 | -0.84 | -0.92 – -0.77 | <0.001 |
| Type (FD patient) | 8.22 | 7.40 – 9.03 | <0.001 | 35.91 | 32.10 – 39.73 | <0.001 | -6.82 | -12.06 – -1.58 | 0.011 |
| Sex (Male) | 3.39 | 2.98 – 3.80 | <0.001 | 5.07 | 3.33 – 6.80 | <0.001 | -3.93 | -6.05 – -1.80 | <0.001 |
| <i>Model 2 (Controls and FD patients combined groups- with age*Type*Sex interactions)</i> | | | | | | | | | |
| (Intercept) | 7.94 | 7.05 – 8.82 | | 28.73 | 25.17 – 32.30 | | 77.72 | 72.99 – 82.44 | |
| Age | 0.06 | 0.04 – 0.08 | <0.001 | 0.37 | 0.29 – 0.45 | <0.001 | -0.74 | -0.84 – -0.63 | <0.001 |
| Type (FD patient) | 2.87 | 0.22 – 5.51 | 0.034 | -57.61 | -69.01 – -46.21 | <0.001 | 5.00 | -10.16 – 20.16 | 0.518 |
| Sex (Male) | 5.95 | 4.54 – 7.37 | <0.001 | 3.63 | -2.08 – 9.34 | 0.213 | 4.42 | -3.11 – 11.96 | 0.250 |
| Age*Type (FD patient) | 0.12 | 0.07 – 0.18 | <0.001 | 2.40 | 2.14 – 2.66 | <0.001 | -0.40 | -0.74 – -0.06 | 0.020 |
| Age*Sex (Male) | -0.06 | -0.09 – -0.03 | <0.001 | 0.06 | -0.07 – 0.19 | 0.344 | -0.20 | -0.37 – -0.04 | 0.017 |
| Type (FD patient)*Sex (Male) | -4.25 | -8.33 – -0.17 | 0.041 | -8.01 | -25.69 – 9.68 | 0.375 | 8.42 | -15.54 – 32.39 | 0.491 |
| Age*Type (FD patient)*Sex (Male) | 0.14 | 0.04 – 0.23 | 0.005 | 0.11 | -0.32 – 0.54 | 0.619 | -0.20 | -0.76 – 0.36 | 0.477 |

| Supplemental table 1C | | | | |
|--|----------------------|--------------------|---------------------|---------------------|
| Conduction times - estimated regression coefficients (β) per 10 years increase in age in ERT treated versus ERT treated and untreated FD patients with 95%-CI (based on the GLM) | | | | |
| * <i>p</i> < 0.05, ** <i>p</i> < 0.01, *** <i>p</i> <0.001 | | | | |
| ERT treated | P-wave duration (ms) | PR-interval (ms) | QRS-duration (ms) | QTc (ms) |
| FD men | 2.7 (1.5-4.0)*** | 2.1 (-1.2-5.4) | 10.9 (9.3-12.4)*** | 20.8 (18.0-23.5)*** |
| FD women | 5.3 (4.2-6.4)*** | 12.4 (9.5-15.3)*** | 10.1 (8.7- 11.5)*** | 13.8 (11.3-16.2)*** |
| ERT treated and untreated | P-wave duration (ms) | PR-interval (ms) | QRS-duration (ms) | QTc (ms) |
| FD men | 2.9 (1.7-4.2)*** | 2.3 (-1.0-5.5) | 10.5 (8.9-12.0)*** | 20.8 (18.1-23.5)*** |
| FD women | 5.0 (4.0-5.9)*** | 10.4 (7.9-12.9)*** | 9.3 (8.0-10.5)*** | 12.6 (10.5-14.8)*** |

| Supplemental table 1D | | | |
|---|--------------------|-------------------------|-------------------------|
| Other LV ECG parameters - estimated regression coefficients (β) per 10 years increase in age in ERT treated versus ERT treated and untreated FD patients with 95%-CI (based on the GLM) | | | |
| * <i>p</i> < 0.05, ** <i>p</i> < 0.01, *** <i>p</i> <0.001 | | | |
| ERT treated | Cornell index (mm) | Spatial QRS-T angle (°) | Frontal QRS-axis (°) |
| FD men | 2.8 (2.0-3.5)*** | 29.7 (26.4-33.0)*** | -16.2 (-20.6- -11.8)*** |
| FD women | 1.6 (1.0-2.2)*** | 28.5 (25.6- 31.4)*** | -11.9 (-15.6- -8.1)*** |
| ERT treated and untreated | Cornell index (mm) | Spatial QRS-T angle (°) | Frontal QRS-axis (°) |
| FD men | 2.6 (1.9-3.4)*** | 29.4 (26.1-32.6)*** | -15.5 (-19.7- -11.2)*** |
| FD women | 1.8 (1.3-2.4)*** | 27.7 (25.2-30.2)*** | -11.4 (-14.6- -8.2)*** |

| Supplemental table 2: ECG descriptives per age decade (the last available ECG per FD patient per decade was selected to ensure that the influence of repeated measurements was limited). | | | | | | | | | | | |
|--|--------------------------------|------------------------|------------------------------------|----------------------------|---------------------|-------------------------------|----------------------------------|--------------------------|--------------------------------------|------------------------------|---------------------|
| * $p<0.05$, ** $p<0.01$, *** $p<0.001$ | | | | | | | | | | | |
| P-wave duration in men (ms) | | | | | | P-wave duration in women (ms) | | | | | |
| Age category | Available ECGs in Fabry men, n | Fabry men Median (IQR) | Available ECGs in Controls- men, n | Controls- men Median (IQR) | P- value | Age category | Available ECGs in Fabry women, n | Fabry women Median (IQR) | Available ECGs in Controls- women, n | Controls- women Median (IQR) | P- value |
| 18-29 | 25 | 110 (102-118) | 262 | 108 (102-116) | 1.0 | 18-29 | 28 | 105 (97-111) | 435 | 104 (96-110) | 1.0 |
| 30-39 | 13 | 120 (108-122) | 379 | 112 (106-118) | 0.2 | 30-39 | 21 | 108 (102-114) | 393 | 106 (98-112) | 1.0 |
| 40-49 | 15 | 126 (120-128) | 374 | 116 (110-122) | 0.01* | 40-49 | 32 | 110 (102-120) | 463 | 108 (100-114) | 1.0 |
| 50-59 | 9 | 128 (114-130) | 409 | 118 (112-124) | 1.0 | 50-59 | 32 | 116 (110-129) | 519 | 112 (104-118) | 0.03* |
| 60-69 | 1 | 150 (-) | 235 | 121 (112-128) | 0.4 | 60-69 | 9 | 122 (116-128) | 399 | 114 (106-120) | 0.1 |
| 70+ | - | - | - | - | - | 70+ | 1 | 156 (-) | 11 | 112 (102-121) | 0.9 |
| PR-interval in men (ms) | | | | | | PR-interval in women (ms) | | | | | |
| Age category | Available ECGs in Fabry men, n | Fabry men Median (IQR) | Available ECGs in Controls- men, n | Controls- men Median (IQR) | P- value | Age category | Available ECGs in Fabry women, n | Fabry women Median (IQR) | Available ECGs in Controls- women, n | Controls- women Median (IQR) | P- value |
| 18-29 | 25 | 146 (138-158) | 262 | 156 (142-170) | 0.6 | 18-29 | 28 | 132 (124-143) | 435 | 146 (134-160) | 0.004** |
| 30-39 | 13 | 152 (132-176) | 379 | 158 (144-174) | 1.0 | 30-39 | 21 | 134 (126-162) | 393 | 152 (140-164) | 0.1 |
| 40-49 | 15 | 144 (134-149) | 374 | 162 (150-176) | 0.02* | 40-49 | 32 | 140 (122-155) | 463 | 152 (140-166) | 0.01* |
| 50-59 | 9 | 146 (132-162) | 409 | 166 (152-178) | 0.1 | 50-59 | 32 | 158 (132-177) | 519 | 158 (144-172) | 1.0 |
| 60-69 | 1 | 186 (-) | 235 | 168 (152-188) | 1.0 | 60-69 | 9 | 180 (170-184) | 399 | 158 (146-174) | 0.1 |
| 70+ | - | - | - | - | - | 70+ | 1 | 244 (-) | 11 | 166 (146-174) | 0.9 |
| QRS-duration in men (ms) | | | | | | QRS-duration in women (ms) | | | | | |
| Age category | Available ECGs in Fabry men, n | Fabry men Median (IQR) | Available ECGs in Controls- men, n | Controls- men Median (IQR) | P- value | Age category | Available ECGs in Fabry women, n | Fabry women Median (IQR) | Available ECGs in Controls- women, n | Controls- women Median (IQR) | P- value |
| 18-29 | 25 | 104 (94-108) | 262 | 102 (96-108) | 1.0 | 18-29 | 28 | 87 (84-94) | 435 | 92 (86-98) | 0.06 |
| 30-39 | 13 | 102 (96-114) | 379 | 102 (96-108) | 1.0 | 30-39 | 21 | 96 (86-100) | 393 | 90 (86-96) | 1.0 |
| 40-49 | 18 | 113 (105-137) | 374 | 102 (96-106) | <0.001*** | 40-49 | 34 | 97 (88-106) | 463 | 90 (86-97) | 0.02* |
| 50-59 | 15 | 134 (121-149) | 415 | 100 (94-106) | <0.001*** | 50-59 | 38 | 108 (99-116) | 519 | 92 (86-98) | <0.001*** |
| 60-69 | 3 | 166 (159-184) | 237 | 100 (94-106) | 0.02* | 60-69 | 16 | 117 (96-145) | 405 | 92 (86-98) | <0.001*** |
| 70+ | - | - | - | - | - | 70+ | 4 | 152 (136-173) | 11 | 90 (85-98) | 0.04* |
| QTc in men (ms) | | | | | | QTc in women (ms) | | | | | |
| Age category | Available ECGs in Fabry men, n | Fabry men Median (IQR) | Available ECGs in Controls- men, n | Controls- men Median (IQR) | P- value | Age category | Available ECGs in Fabry women, n | Fabry women Median (IQR) | Available ECGs in Controls- women, n | Controls- women Median (IQR) | P- value |
| 18-29 | 25 | 388 (373-398) | 262 | 405 (387-418) | 0.02* | 18-29 | 28 | 394 (385-413) | 435 | 412 (399-424) | <0.001*** |
| 30-39 | 13 | 414 (410-431) | 379 | 407 (394-422) | 0.3 | 30-39 | 21 | 410 (396-423) | 393 | 418 (406-432) | 0.2 |
| 40-49 | 18 | 428 (420-452) | 374 | 411 (396-424) | 0.001** | 40-49 | 34 | 424 (402-432) | 463 | 421 (409-435) | 1.0 |
| 50-59 | 15 | 438 (414-478) | 415 | 416 (402-430) | 0.02* | 50-59 | 38 | 429 (417-449) | 519 | 424 (411-437) | 0.08 |
| 60-69 | 3 | 492 (475-517) | 237 | 422 (405-436) | 0.02* | 60-69 | 16 | 456 (424-485) | 405 | 429 (417-445) | 0.1 |
| 70+ | - | - | - | - | - | 70+ | 4 | 496 (478-527) | 11 | 428 (419-444) | 0.009** |

| Cornell index in men (ms) | | | | | | Cornell index in women (ms) | | | | | |
|--------------------------------|--------------------------------|------------------------|------------------------------------|----------------------------|---------------------|----------------------------------|----------------------------------|--------------------------|--------------------------------------|------------------------------|---------------------|
| Age category | Available ECGs in Fabry men, n | Fabry men Median (IQR) | Available ECGs in Controls- men, n | Controls- men Median (IQR) | P- value | Age category | Available ECGs in Fabry women, n | Fabry women Median (IQR) | Available ECGs in Controls- women, n | Controls- women Median (IQR) | P- value |
| 18-29 | 25 | 19 (15-22) | 262 | 14 (10-18) | 0.004** | 18-29 | 28 | 12 (9-14) | 435 | 9 (6-12) | 0.3 |
| 30-39 | 13 | 17 (12-26) | 379 | 13 (9-17) | 0.1 | 30-39 | 21 | 14 (9-20) | 393 | 10 (7-13) | 0.008** |
| 40-49 | 18 | 27 (16-34) | 374 | 13 (10-17) | <0.001*** | 40-49 | 34 | 21 (13-30) | 463 | 9 (7-13) | <0.001*** |
| 50-59 | 15 | 25 (21-32) | 415 | 14 (9-17) | <0.001*** | 50-59 | 38 | 20 (13-29) | 519 | 10 (7-13) | <0.001*** |
| 60-69 | 3 | 19 (15-23) | 237 | 14 (11-18) | 1.0 | 60-69 | 16 | 20 (14-23) | 405 | 13 (9-16) | 0.003** |
| 70+ | - | - | - | - | - | 70+ | 4 | 13 (6-19) | 11 | 13 (10-14) | 1.0 |
| Spatial QRS-T angle in men (°) | | | | | | Spatial QRS-T angle in women (°) | | | | | |
| Age category | Available ECGs in Fabry men, n | Fabry men Median (IQR) | Available ECGs in Controls- men, n | Controls- men Median (IQR) | P- value | Age category | Available ECGs in Fabry women, n | Fabry women Median (IQR) | Available ECGs in Controls- women, n | Controls- women Median (IQR) | P- value |
| 18-29 | 25 | 33 (24-40) | 262 | 42 (28-57) | 0.09 | 18-29 | 28 | 29 (20-37) | 435 | 37 (25-48) | 0.1 |
| 30-39 | 13 | 37 (24-126) | 379 | 45 (31-60) | 1.0 | 30-39 | 21 | 31 (22-60) | 393 | 38 (28-50) | 1.0 |
| 40-49 | 18 | 137 (98-159) | 374 | 47 (35-63) | <0.001*** | 40-49 | 34 | 148 (111-161) | 463 | 42 (31-56) | <0.001*** |
| 50-59 | 15 | 148 (122-154) | 415 | 55 (38-71) | <0.001*** | 50-59 | 38 | 154 (126-166) | 519 | 47 (33-60) | <0.001*** |
| 60-69 | 3 | 149 (79-155) | 237 | 54 (43-75) | 1.0 | 60-69 | 16 | 151 (137-169) | 405 | 49 (36-69) | <0.001*** |
| 70+ | - | - | - | - | - | 70+ | 4 | 157 (139-164) | 11 | 54 (40-73) | 0.03* |
| Frontal QRS-axis in men (°) | | | | | | Frontal QRS-axis in women (°) | | | | | |
| Age category | Available ECGs in Fabry men, n | Fabry men Median (IQR) | Available ECGs in Controls- men, n | Controls- men Median (IQR) | P- value | Age category | Available ECGs in Fabry women, n | Fabry women Median (IQR) | Available ECGs in Controls- women, n | Controls- women Median (IQR) | P- value |
| 18-29 | 25 | 50 (33-61) | 262 | 64 (44-79) | 0.01* | 18-29 | 28 | 47 (30-63) | 434 | 64 (48-76) | 0.008** |
| 30-39 | 13 | 41 (31-55) | 378 | 57 (32-72) | 0.3 | 30-39 | 21 | 37 (21-46) | 393 | 59 (37-71) | 0.03* |
| 40-49 | 18 | 36 (10-50) | 374 | 47 (19-67) | 0.2 | 40-49 | 34 | 32 (11-53) | 463 | 55 (30-70) | 0.002** |
| 50-59 | 15 | 7 (-25-31) | 415 | 33 (5-60) | 0.02* | 50-59 | 38 | 25 (4-46) | 519 | 42 (18-63) | 0.01* |
| 60-69 | 3 | -48 (-57-25) | 237 | 26 (-4-57) | 1.0 | 60-69 | 16 | 21 (-4.0-42) | 404 | 30 (8-52) | 1.0 |
| 70+ | - | - | - | - | - | 70+ | 4 | 50 (1-92) | 11 | 15 (7-20) | 1.0 |

| Supplemental table 3- Definitions of cardiac events [1] | |
|---|--|
| Events | Definition |
| <i>Major adverse cardiovascular events (MACE): composite of cardiovascular death, heart failure hospitalization, sustained ventricular arrhythmias (SVA) and myocardial infarction</i> | |
| 1. Cardiovascular death | <p>Death as a result of one of the following diseases/ syndromes:</p> <ul style="list-style-type: none"> - Acute coronary syndrome - Sudden cardiac death (SCD) - Hypertensive crise - Ischemic or hemorrhagic stroke - Cardiomyopathy - Other cardiovascular cause such as: pulmonary embolism, peripheral vascular disease |
| 2. Heart failure hospitalization | Hospital admission (at least one night) with the following clinical manifestations of heart failure: dyspnea, reduced exercise tolerance, fluid retention in peripheral and/ or splanchnic vessels, seen as peripheral edema |
| 3. Sustained ventricular arrhythmia (SVA) | composite of sudden cardiac death (SCD), sudden cardiac arrest (SCA), sustained ventricular tachycardia (VT) including appropriate ICD shock, and ventricular fibrillation (VF) |
| 4. Myocardial infarction | Acute myocardial injury with clinical evidence of acute myocardial ischemia. Definition according to the Fourth Universal Definition of Myocardial Infarction |

1. El Sayed, M., et al., *Influence of sex and phenotype on cardiac outcomes in patients with Fabry disease*. Heart, 2021.

| Supplemental table 4: GLA mutations frequencies | | |
|--|---------------------------------|-----------------------------------|
| GLA mutation at DNA level | Frequency in FD- men (N) | Frequency in FD- women (N) |
| c.1025G>A | 8 | 13 |
| c.1040dupT | 0 | 2 |
| c.1074_1075del | 1 | 3 |
| c.1118G>A | 1 | 2 |
| c.1124_1176del | 2 | 0 |
| c.1156C>T | 2 | 1 |
| c.1246C>T | 1 | 1 |
| c.136C>T | 0 | 1 |
| c.157_160delAACC | 2 | 1 |
| c.215T>G | 1 | 0 |
| c.269G>A | 0 | 1 |
| c.334C>T | 1 | 1 |
| c.400delT | 0 | 2 |
| c.406G>T | 5 | 4 |
| c.422C>T | 1 | 1 |
| c.53T>C | 1 | 11 |
| c.548G>A | 1 | 3 |
| c.606T>G | 0 | 1 |
| c.62T>C | 0 | 3 |
| c.639+1G>A | 0 | 1 |
| c.658C>T | 5 | 4 |
| c.677G>A | 2 | 3 |
| c.679C>T | 2 | 2 |
| c.680G>A | 1 | 2 |
| c.728_744del | 0 | 4 |
| c.779G>A | 0 | 1 |
| c.803T>C | 2 | 1 |
| c.898C>T | 0 | 4 |
| c.901C>T | 3 | 2 |
| c.908_910delTCA | 0 | 1 |
| c.955_969delinsTTGC | 2 | 1 |
| c.963_964delinsCA | 1 | 2 |
| c.996_999del | 0 | 2 |
| c.997C>T | 0 | 1 |
| Duplication exon 3+4 | 1 | 0 |
| IVS6-2A>T (c.1000-2A>T) | 1 | 2 |

Supplemental figures- legends

Supplemental figure 1: Flowchart for the diagnosis and phenotype allocation in FD; cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL); cerebral autosomal recessive arteriopathy with subcortical infarcts and leucoencephalopathy (CARASIL); electron microscopy (EM); galactosidase alpha (GLA); diastolic interventricular septum thickness (IVSd) [1].

Supplemental figure 2: Source raw data of P-wave duration, PR-interval, QRS-duration and QTc for each study participants subgroup. The shaded areas represent the 95%-CI for the GLM fitted curves.

Supplemental figure 3: Source raw data of Cornell index (Cind), Spatial QRS-T angle and Frontal QRS-axis for each study participants subgroup. The shaded areas represent the 95%-CI for the GLM fitted curves.

Supplemental figure 4: Source raw data of the frontal T-axis for each study participants subgroup. The T-axis' normal value (15°-75°) is represented by the green lines [2].

Supplemental figure 5: Polar plot graphs showing the absolute values of the frontal T-axis for each study participants subgroup. The numbered shells represent the age at which an ECG was obtained. The T-axis' normal value (15°-75°) is represented by the green lines [2].

Supplemental figure 6: Source raw data of the heart rate for each study participants subgroup.

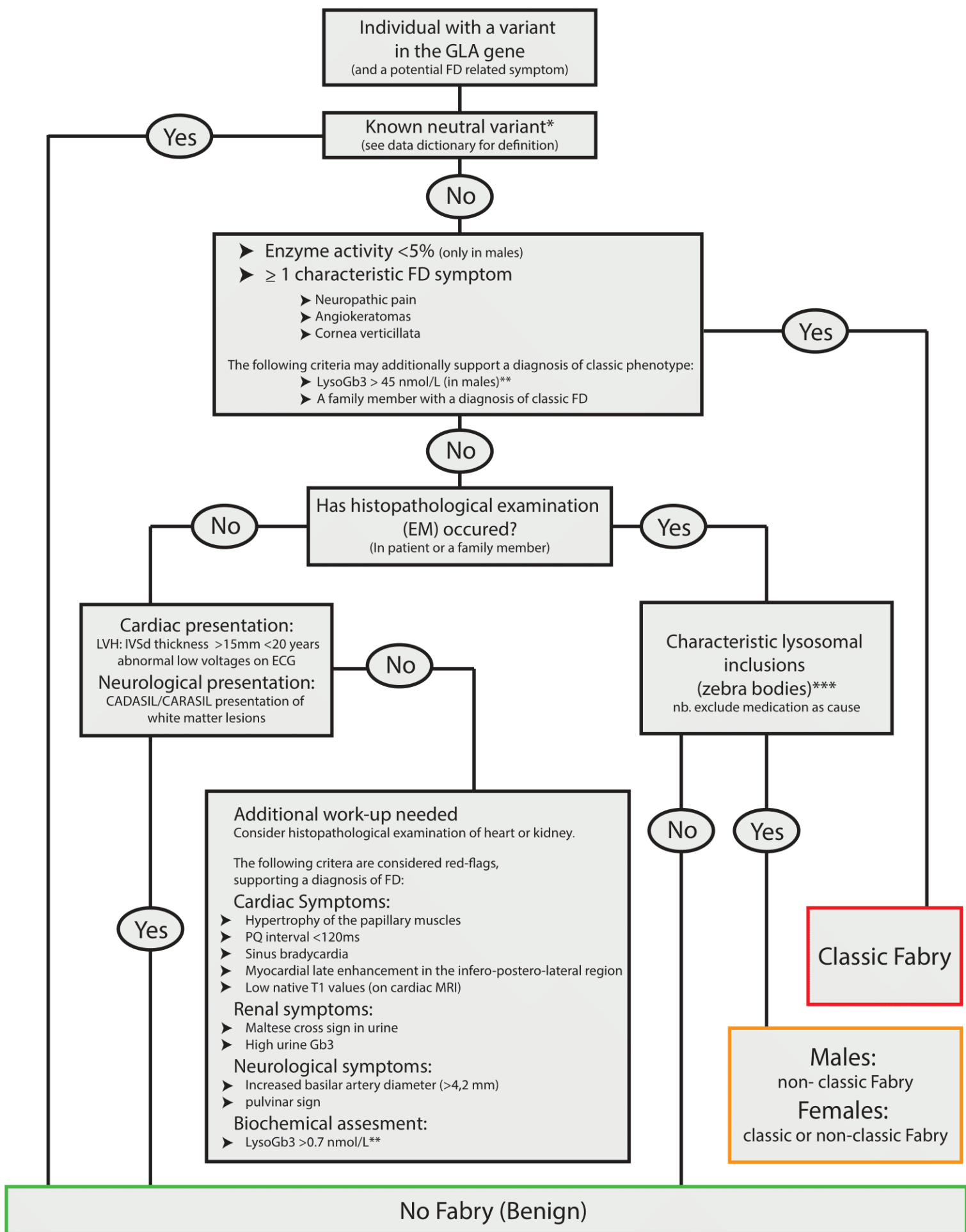
Supplemental figure 7: Boxplots of the heart rate per age decade in Fabry patients and controls. Numbers inside the boxes are the numbers of the analyzed ECGs. The last available ECG per FD patient per decade was selected to ensure that the influence of repeated measurements was limited. The horizontal lines represents the reference range, based on the literature.

Supplemental figure 8: Scatter plot displaying the Spearman correlation between ECG markers obtained from the last ECG and corresponding LVMI on CMR. The shaded areas represent the 95%-CI for the fitted curve.

Supplemental figure 9: Boxplots of the ECG parameters obtained from the last ECG versus the corresponding scored LGE on CMR.

References

1. El Sayed, M., et al., *Influence of sex and phenotype on cardiac outcomes in patients with Fabry disease*. Heart, 2021.
2. Kors, J.A., et al., *T axis as an indicator of risk of cardiac events in elderly people*. The Lancet, 1998. **352**(9128): p. 601-605.

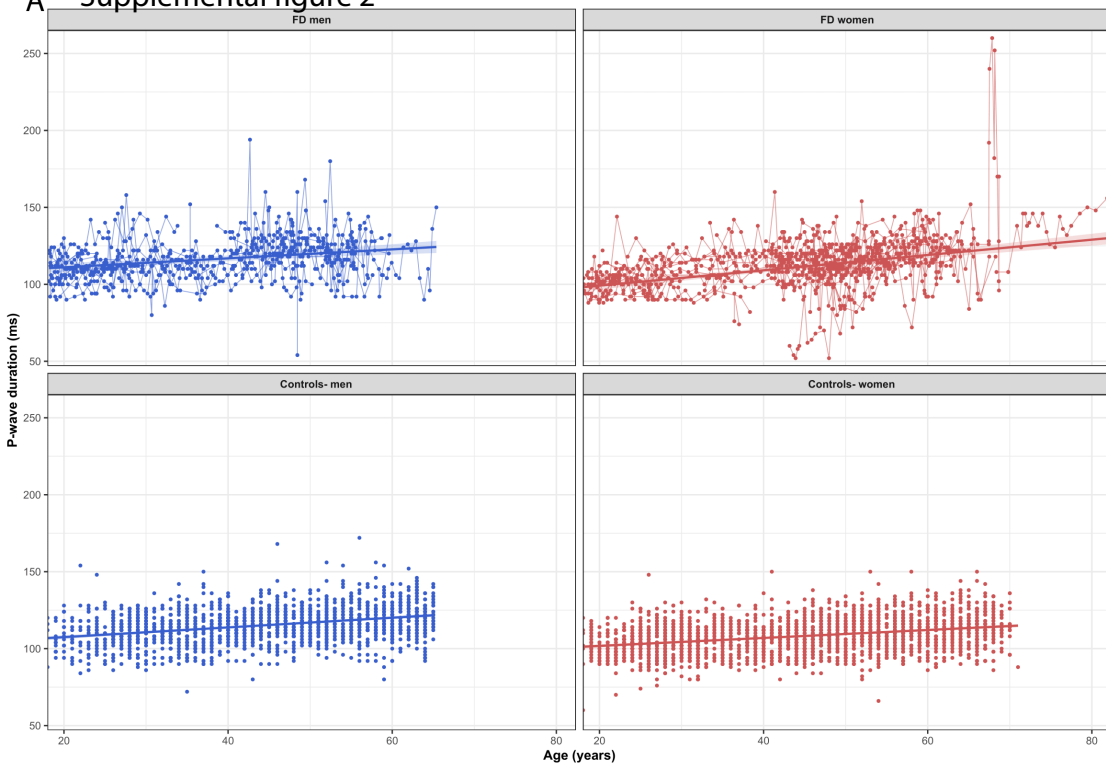
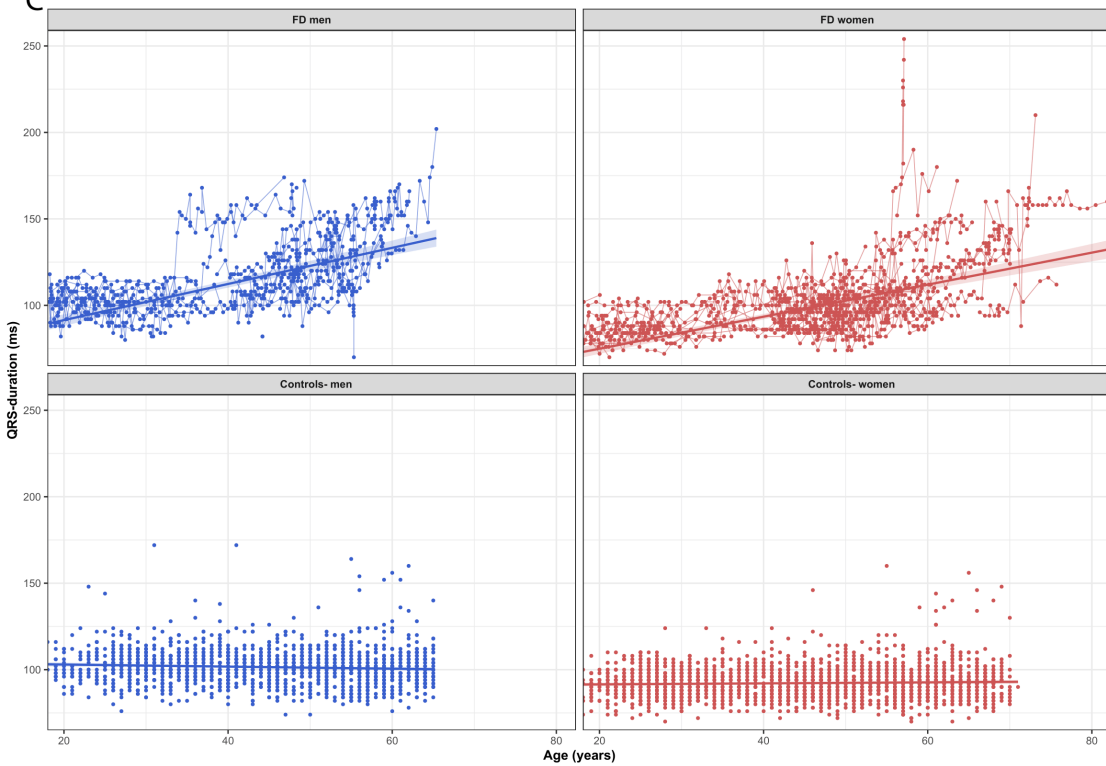
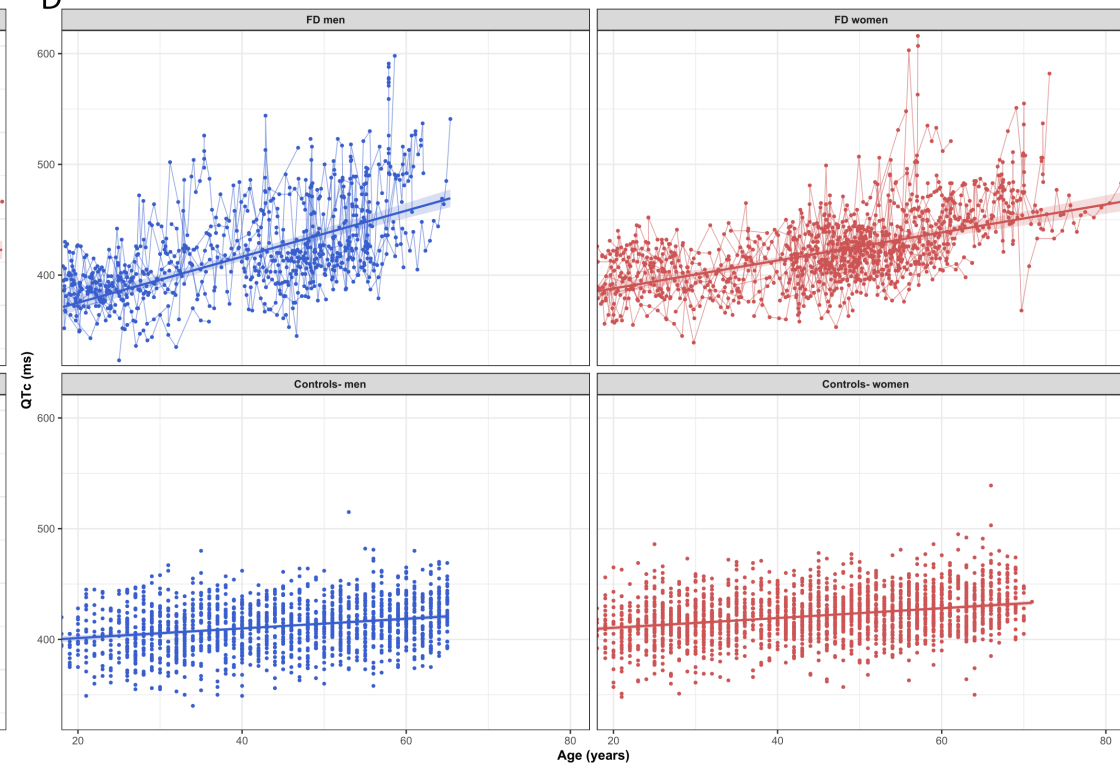


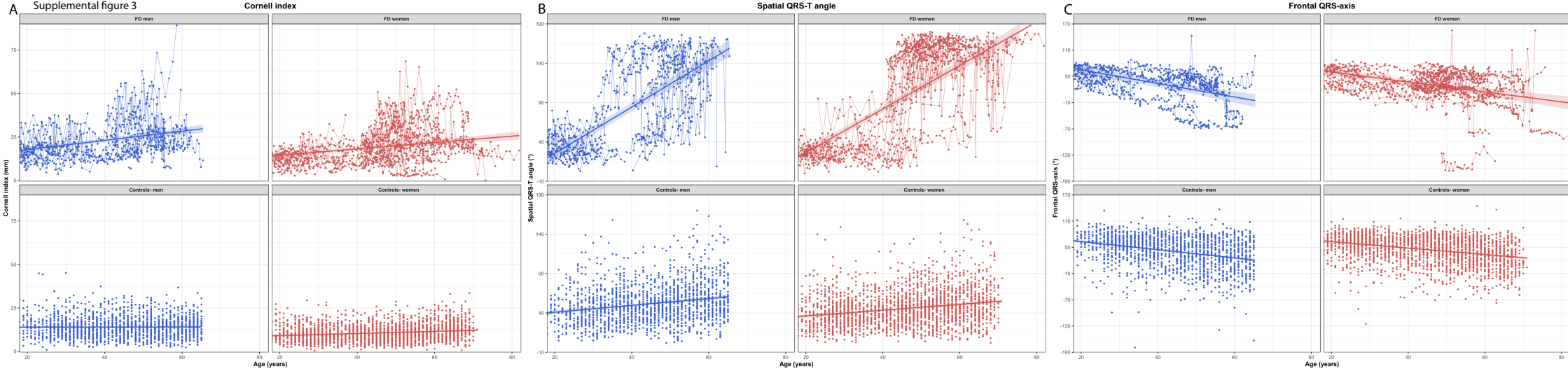
* Known neutral variants by themselves do not cause Fabry disease and thus do not explain the potential FD related symptoms. However the presence of a second, disease causing, variant in the same patient, though very rare, can occur. In case of high clinical suspicion, performing additional diagnostics (lysoGb3 levels, enzyme activity measurement) can thus be considered.

** Plasma lysoGb3 levels may help phenotypic classification (Smid et al 2015, reference values GMD laboratory Amsterdam).

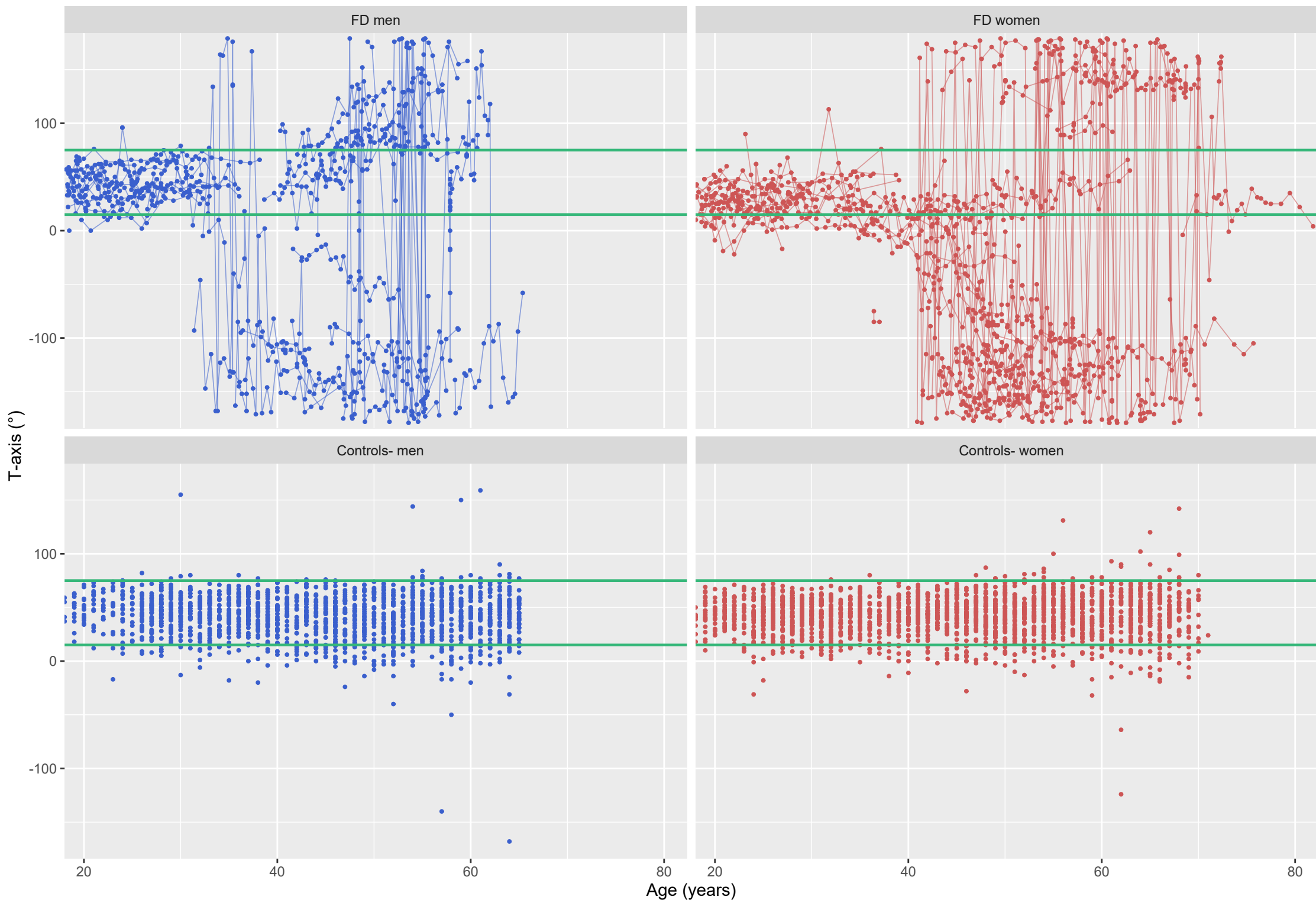
*** Concentric multi-lamellated myelin bodies with a zebra like pattern and a periodicity of aproximately 5nm (Takahashi et al 1987)

This flow-chart is based on several diagnostic algorithms developed by experts. References: Smid et al 2014, van der Tol et al 2014, van der Tol et al 2015.

A Supplemental figure 2**B** PR-interval**C** QRS-duration**D** QTc



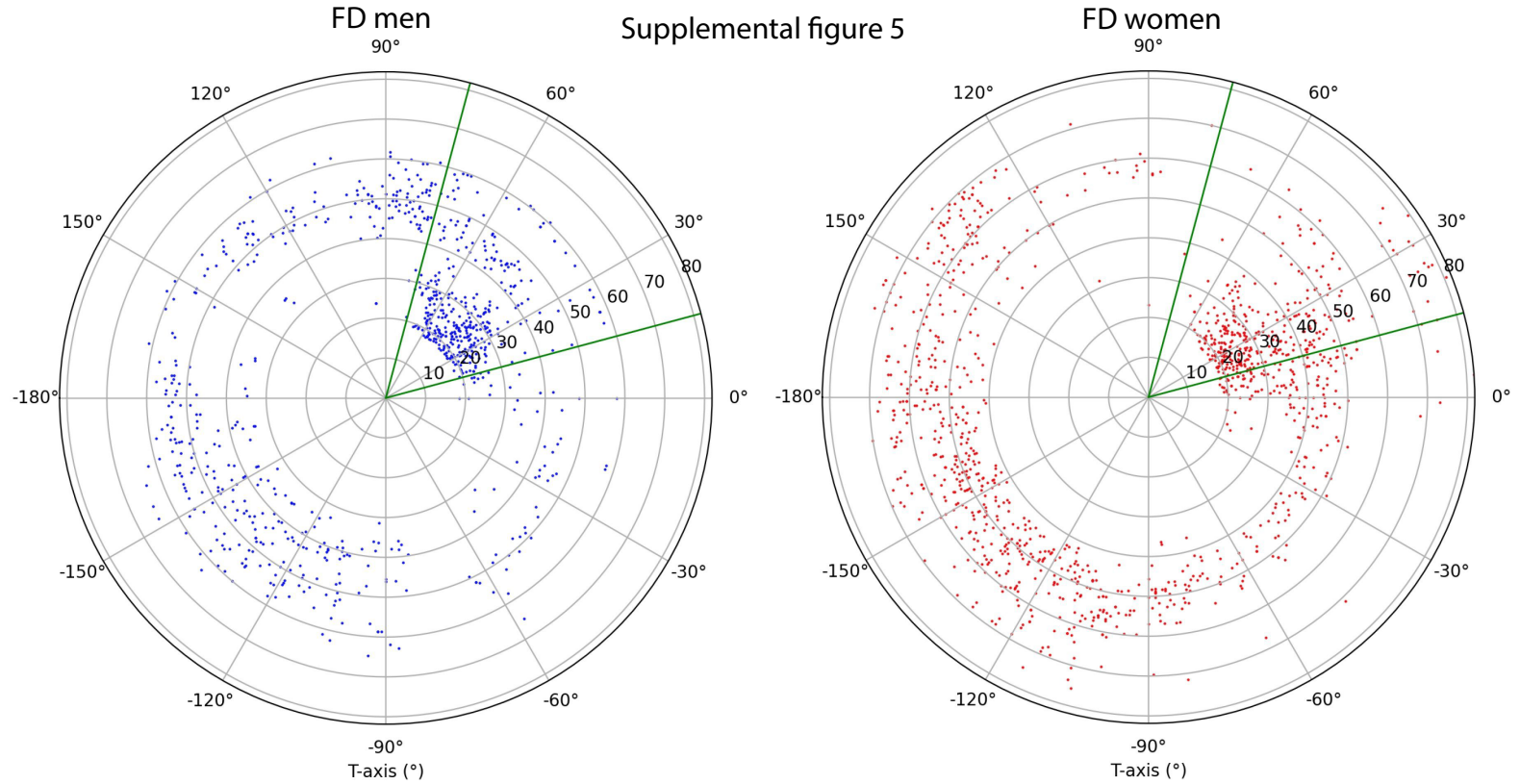
Supplemental figure 4



FD men

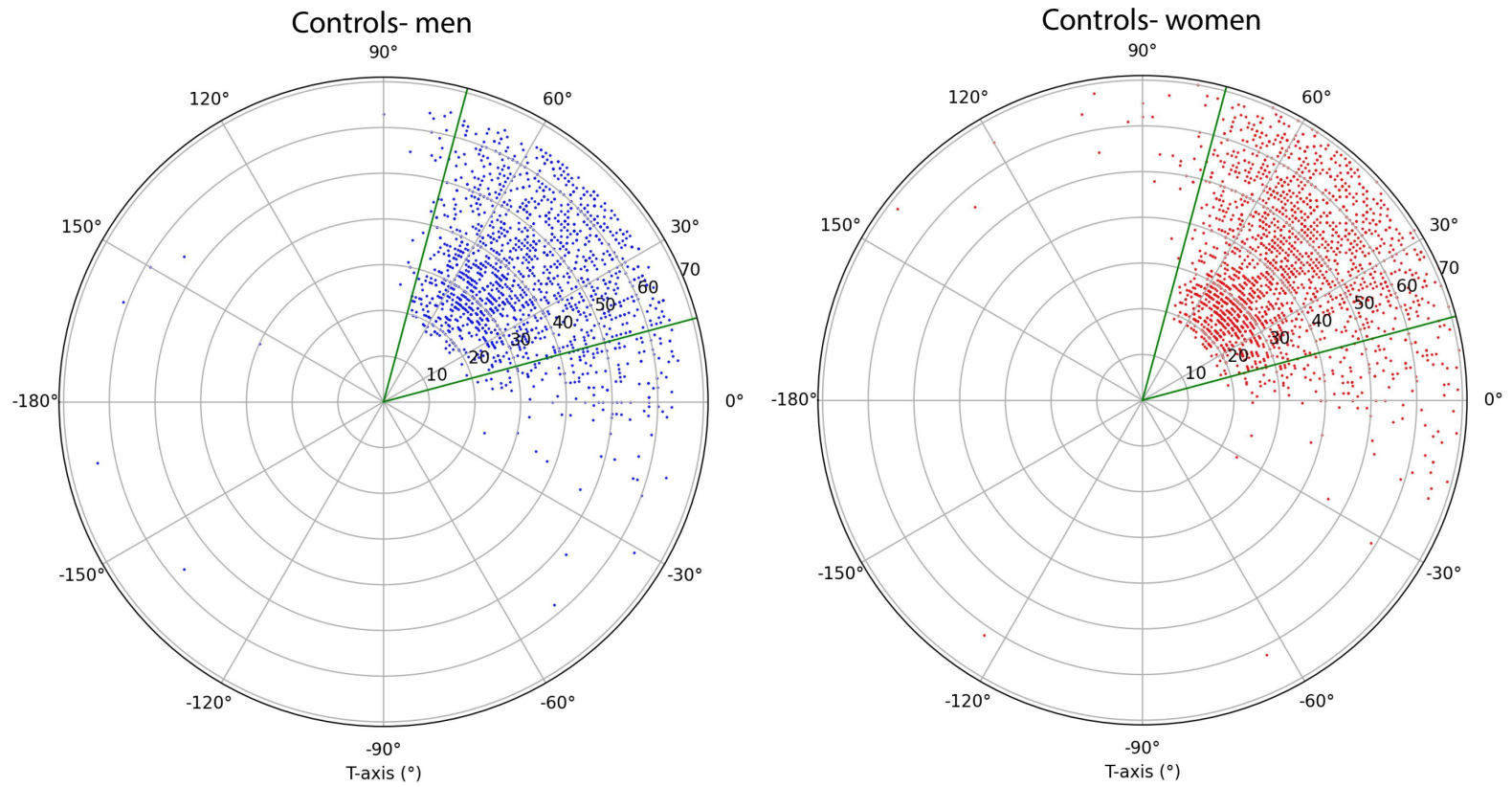
Supplemental figure 5

FD women



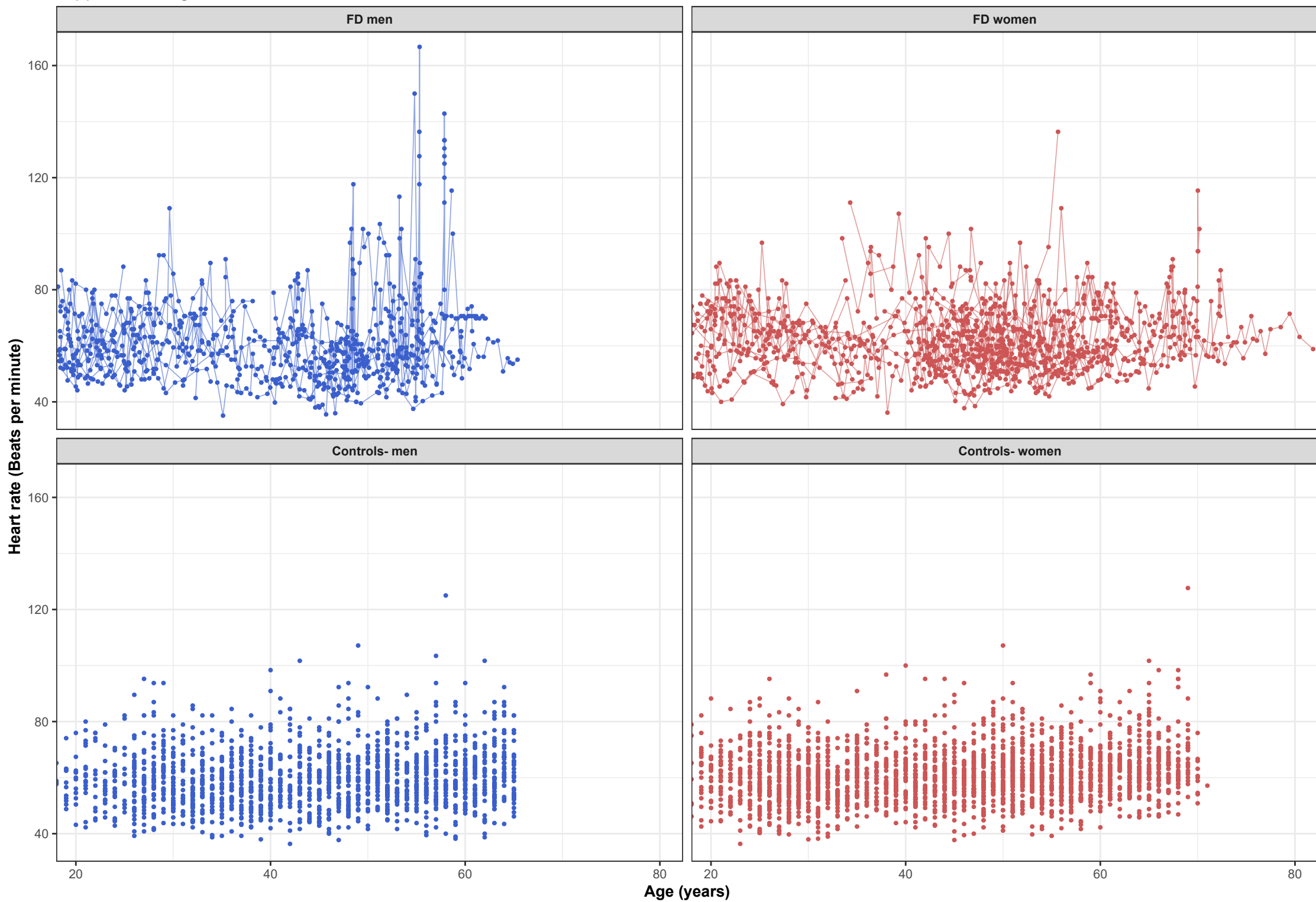
Controls- men

Controls- women



Supplemental figure 6





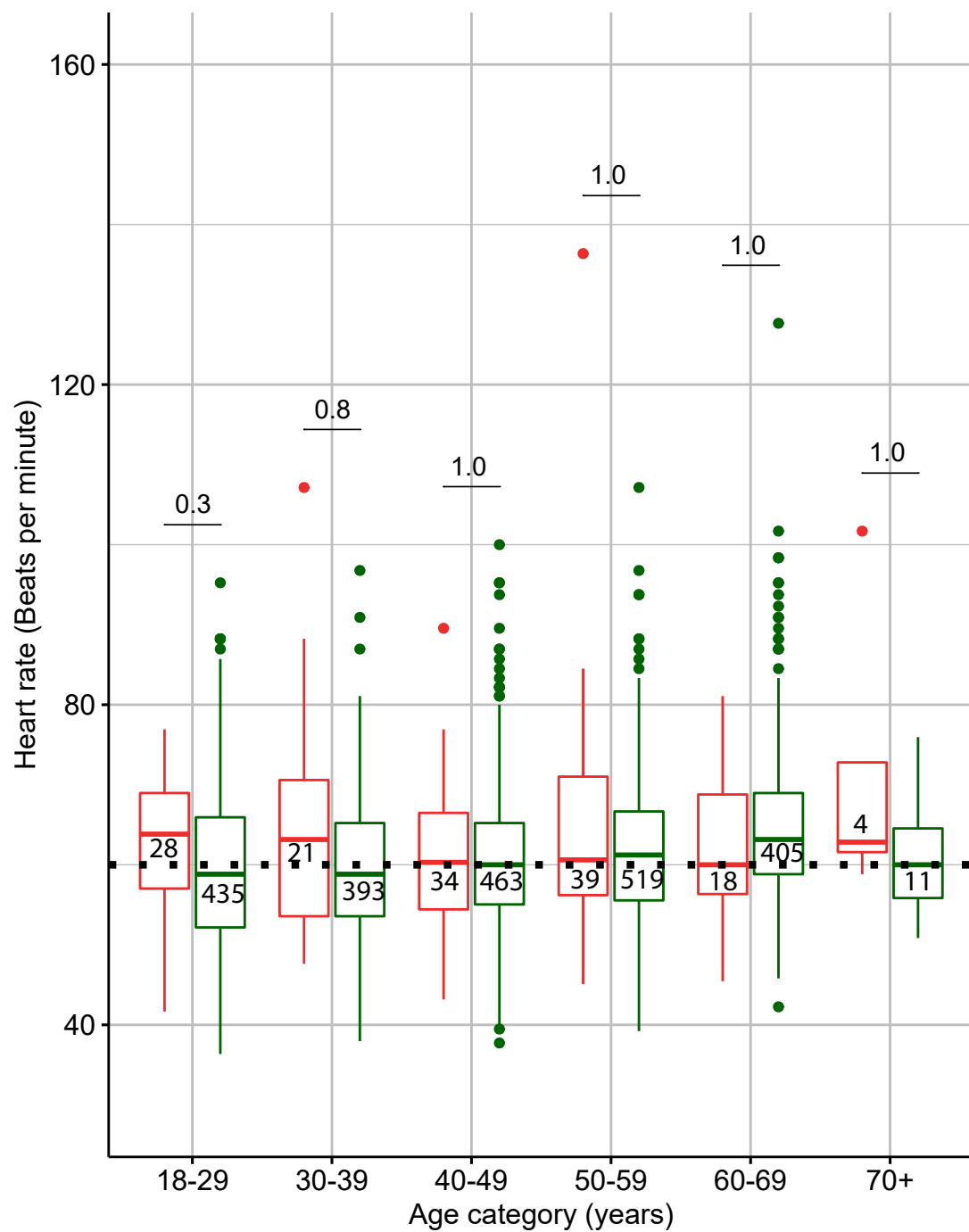
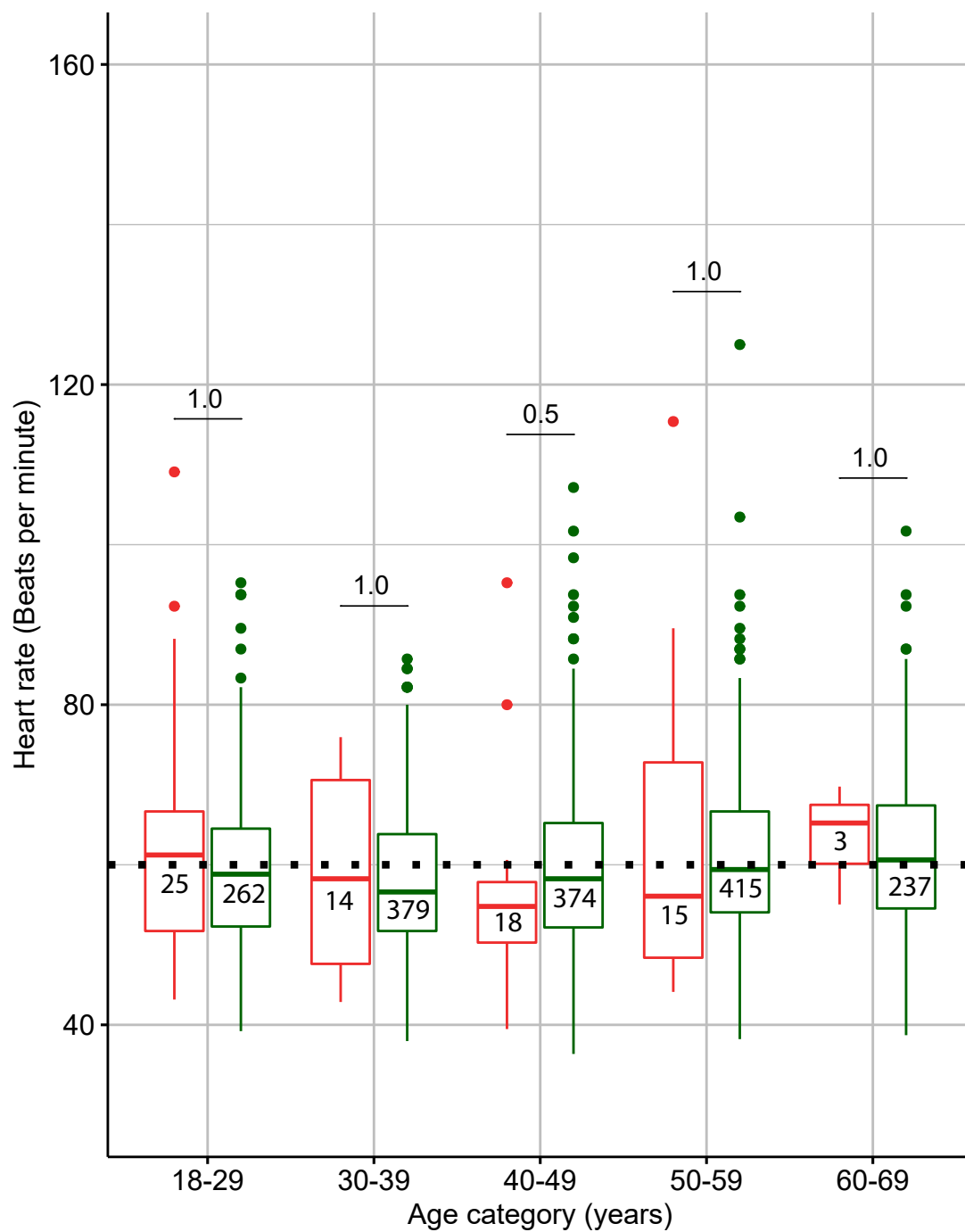
Heart rate



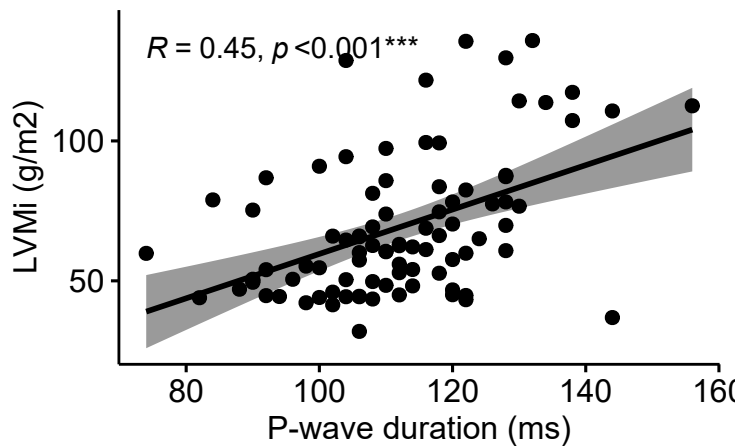
Heart rate in men

Supplemental figure 7

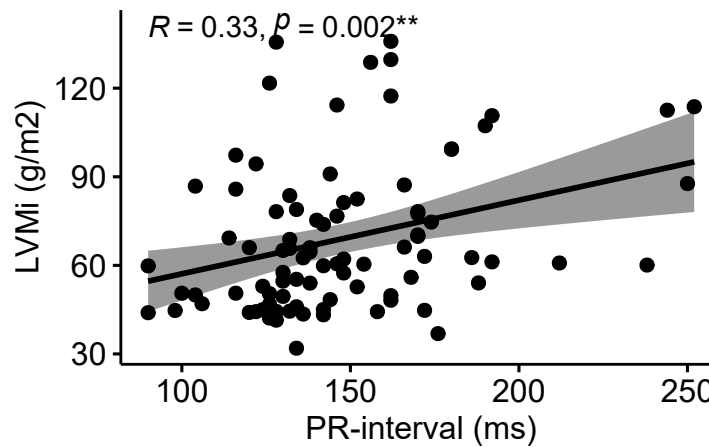
Heart rate in women

Subject  Fabry patient  ControlSubject  Fabry patient  Control

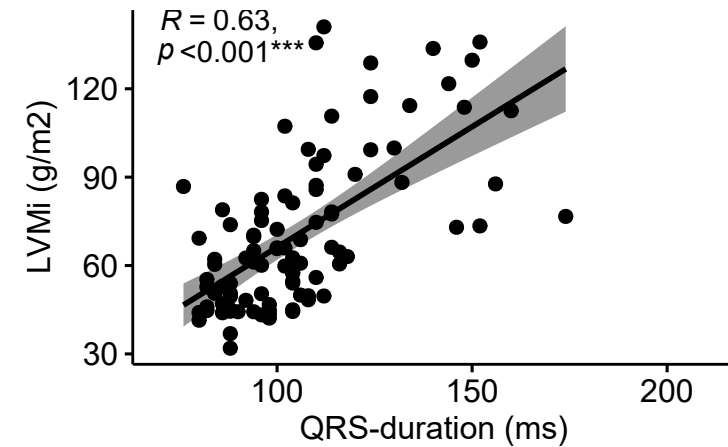
Correlation P-wave duration and LVMi



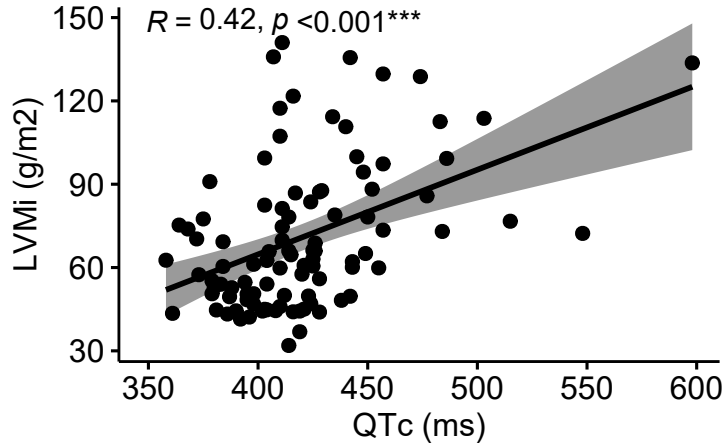
Correlation PR-interval and LVMi



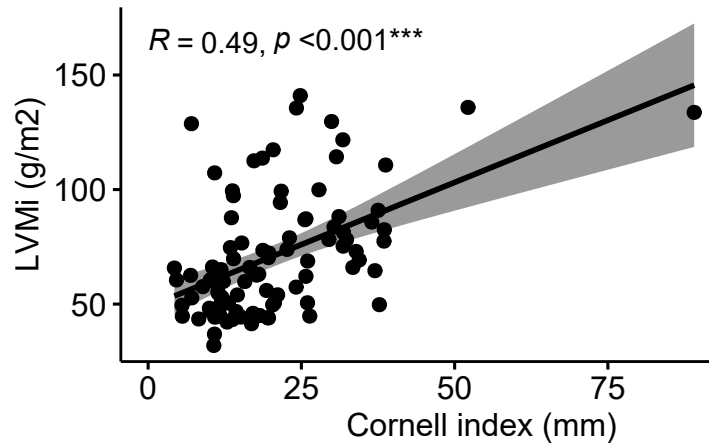
Correlation QRS-duration and LVMi



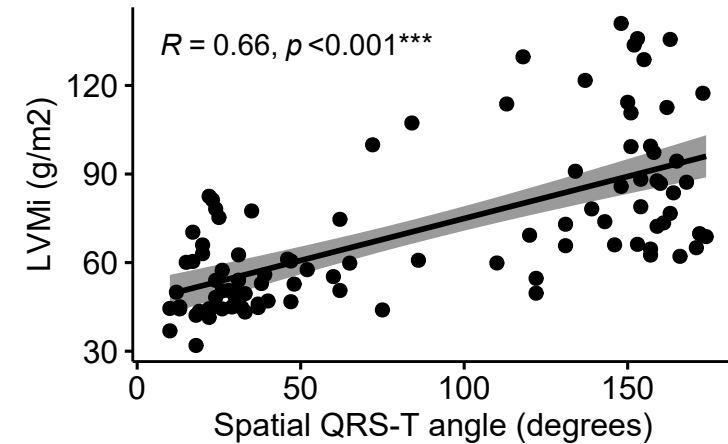
Correlation QTc and LVMi



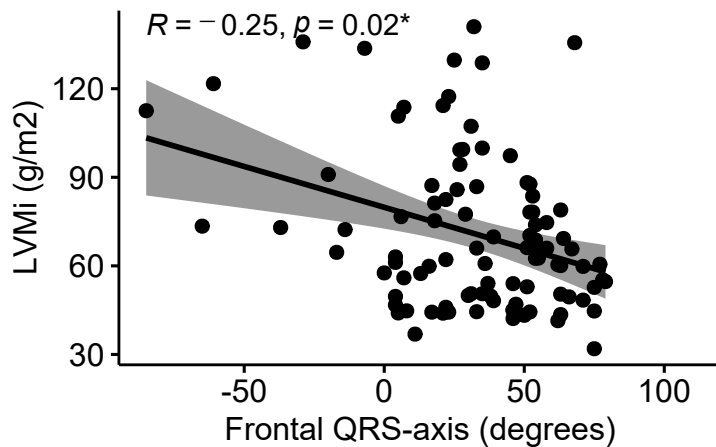
Correlation Cornell index and LVMi



Correlation Spatial QRS-T angle and LVMi

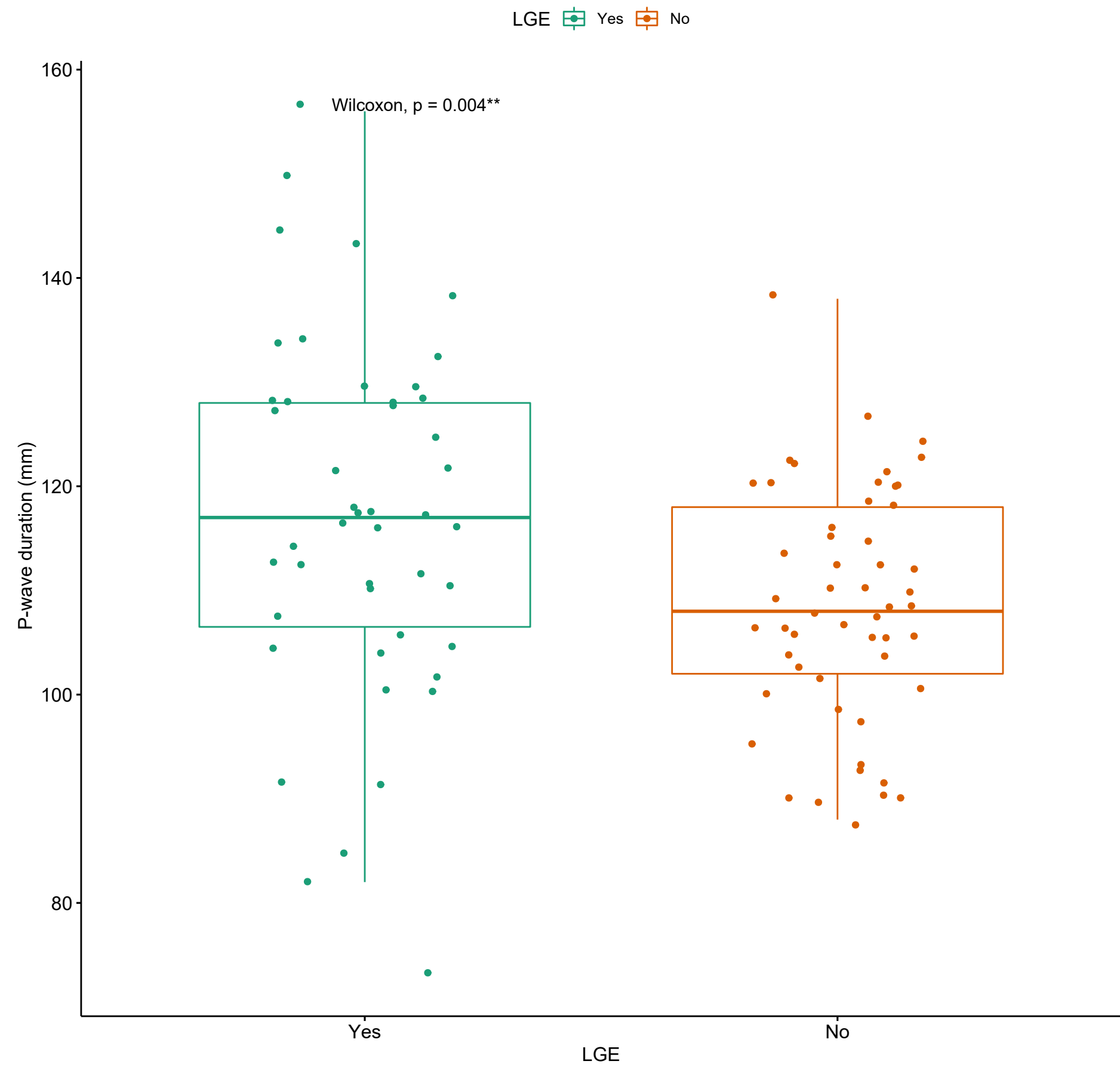


Correlation Frontal QRS-axis and LVMi

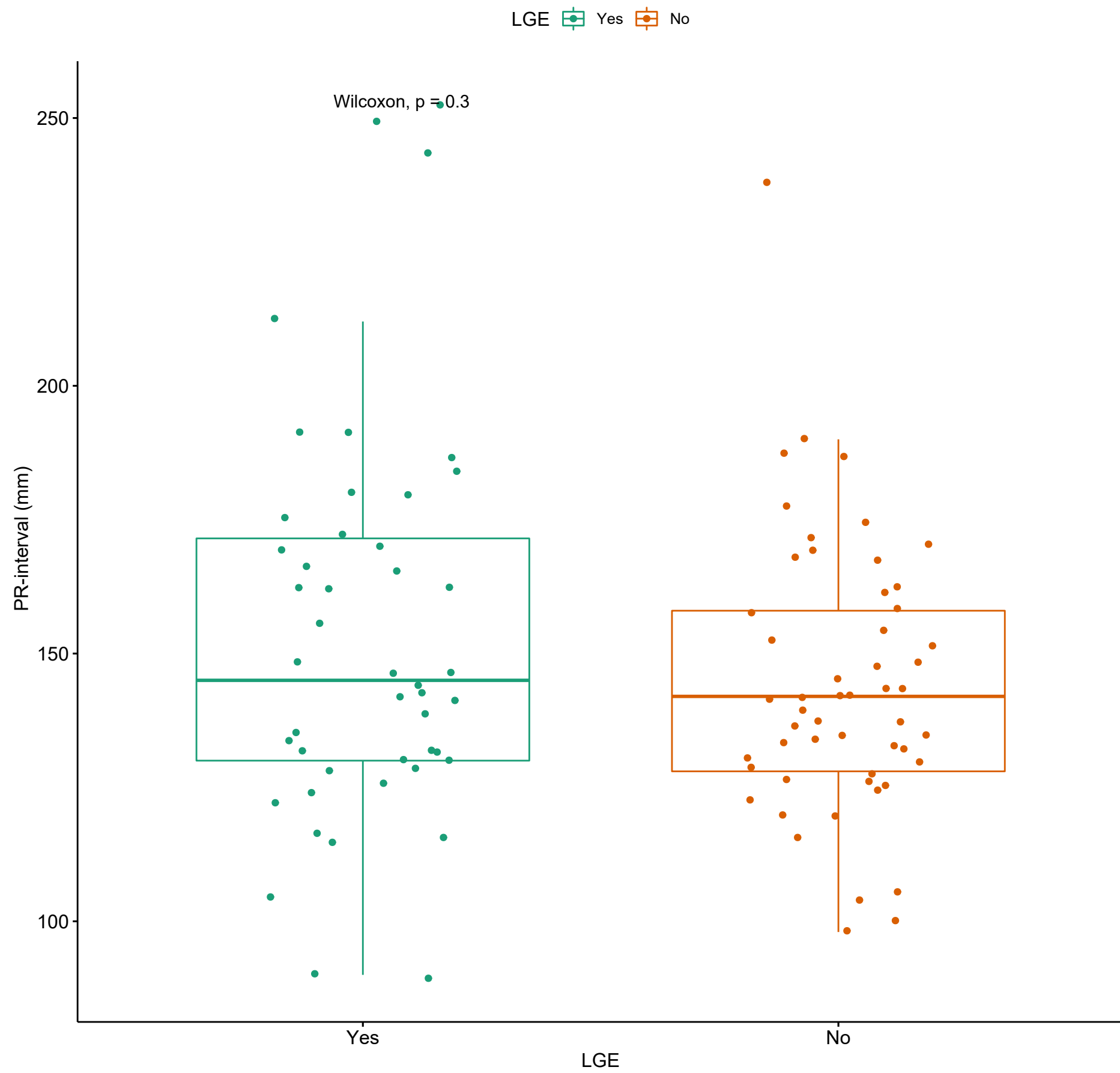


Supplemental figure 8

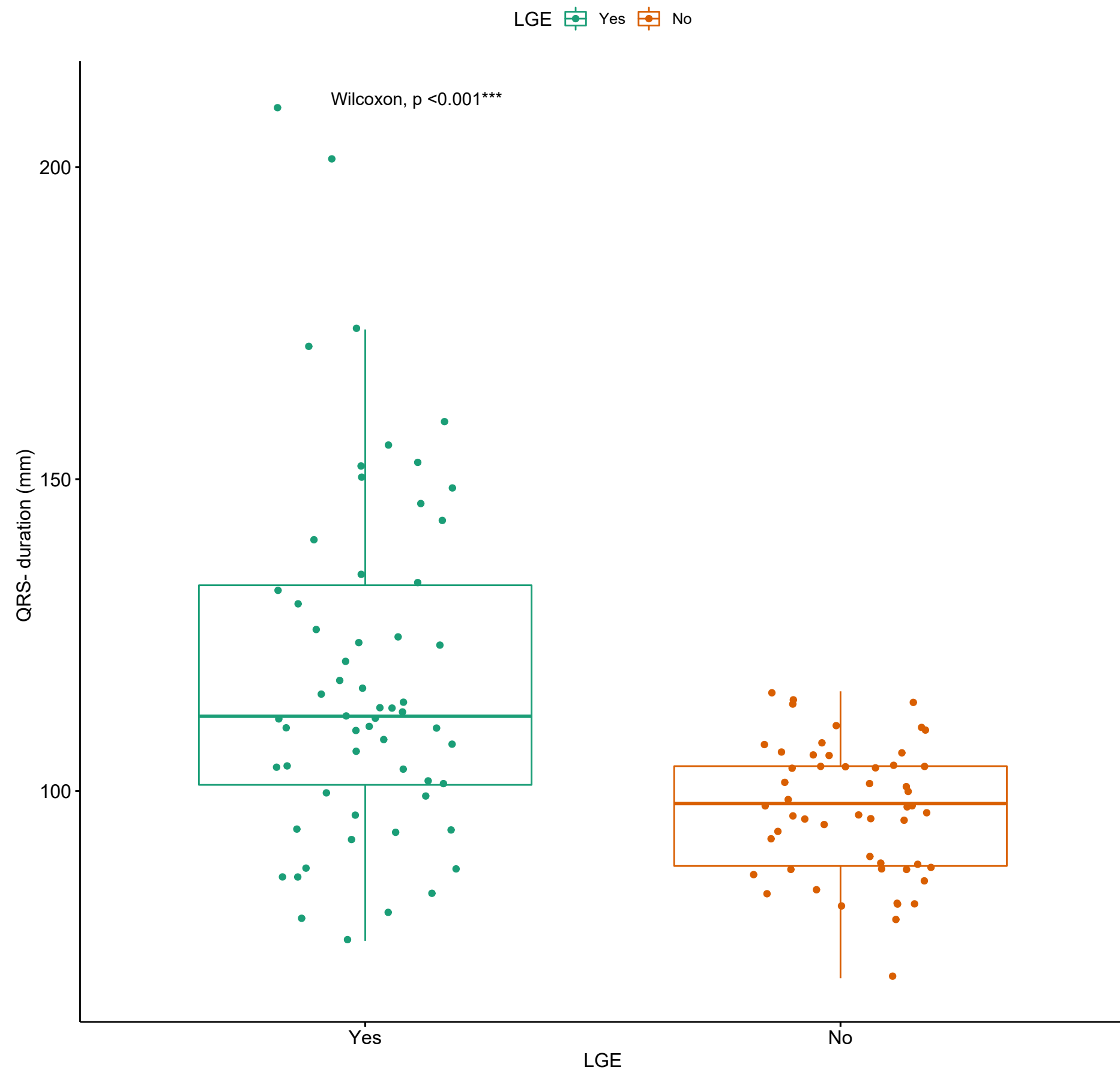
P-wave duration and LGE



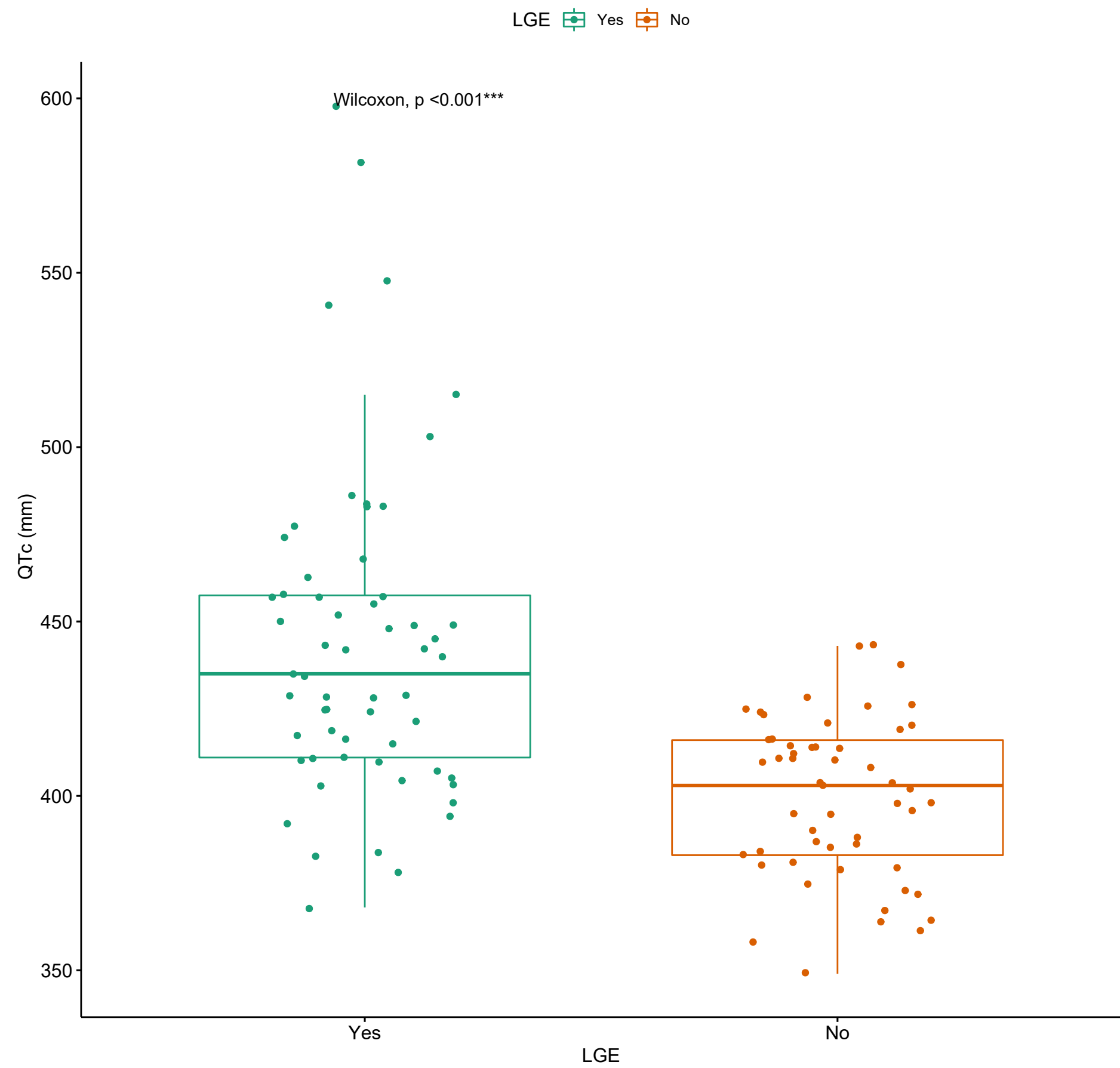
PR-interval and LGE



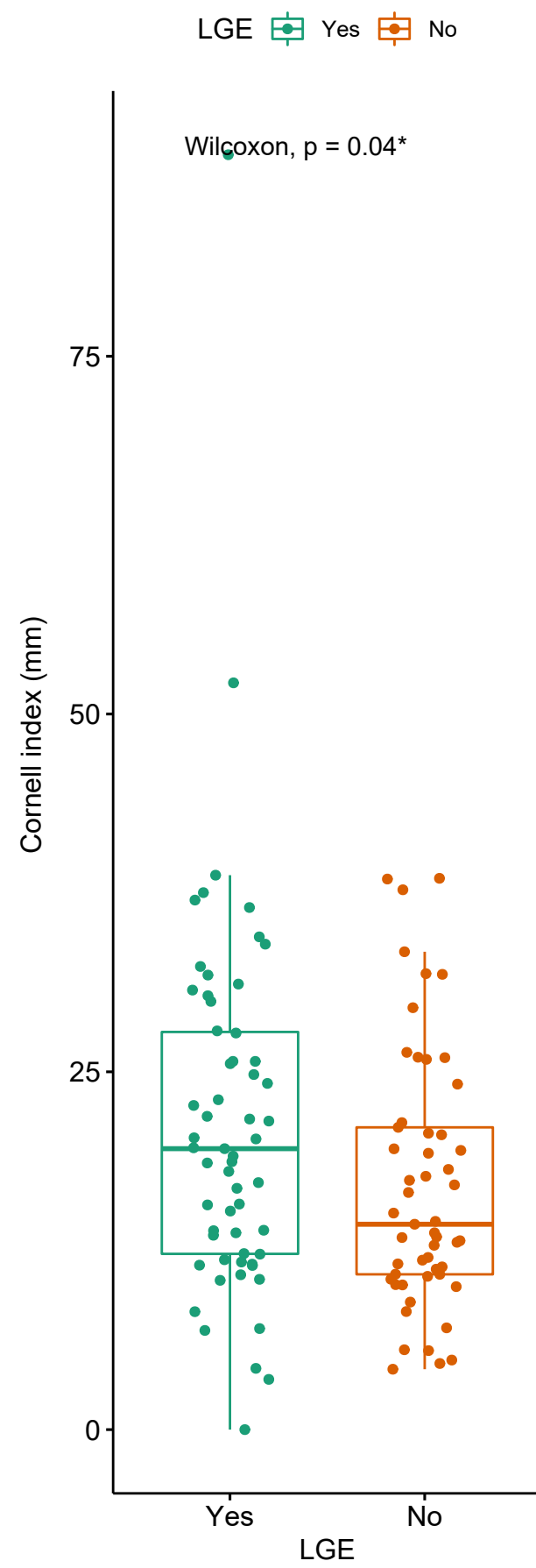
QRS-duration and LGE



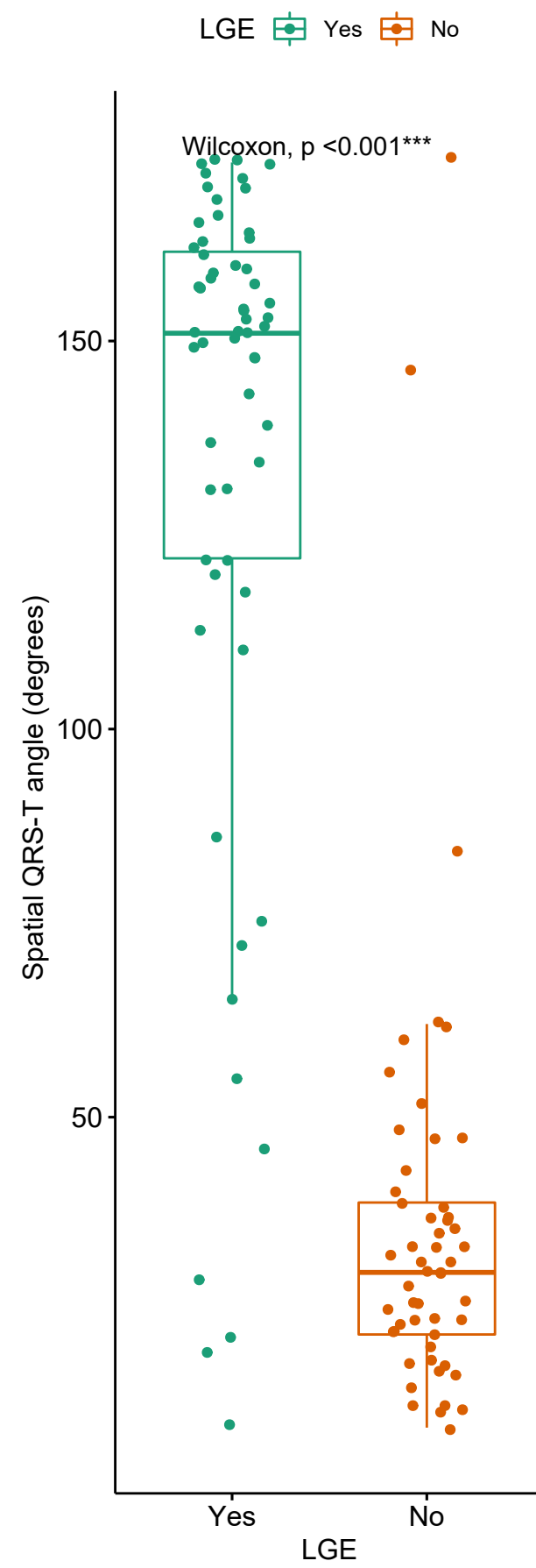
QTc and LGE



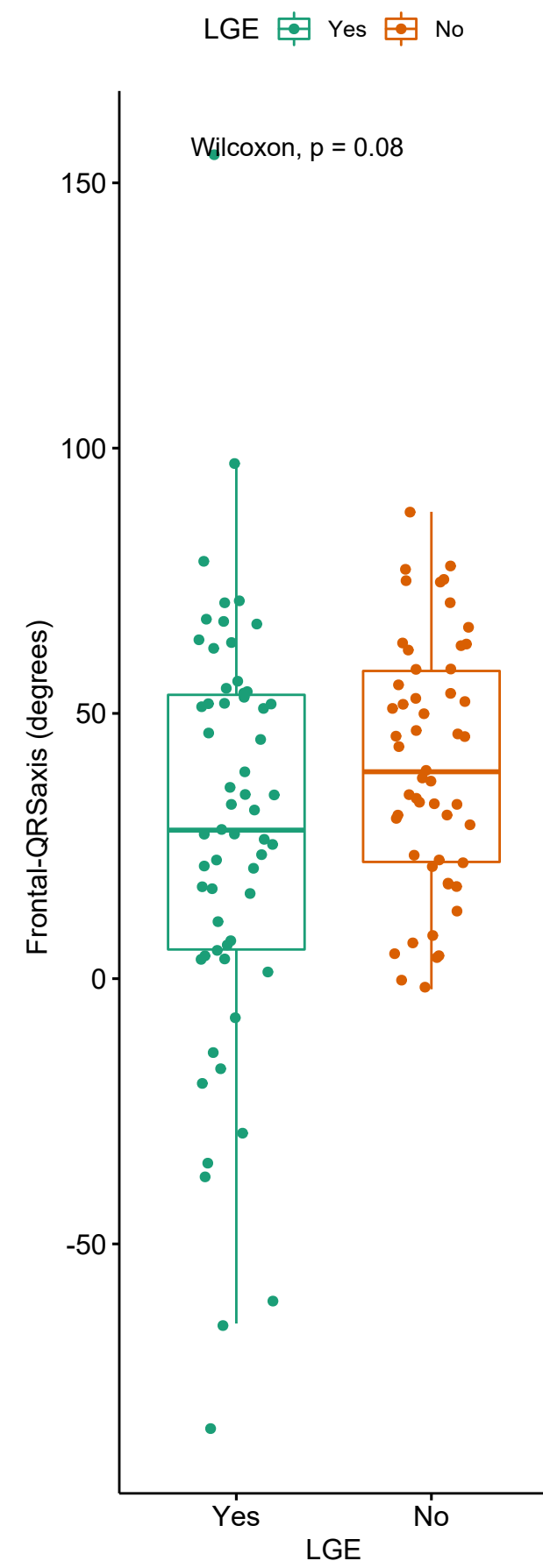
Cornell index and LGE



Spatial QRS-T angle and LGE



Frontal QRS-axis and LGE



Supplemental figure 9