

**Supplemental Table S1. Characteristics of the study population (Screening).**

| <b>Variable</b>                                            | <b>Tertile 1<br/>N = 8</b> | <b>Tertile 3<br/>N = 8</b> | <b>P-value</b> |
|------------------------------------------------------------|----------------------------|----------------------------|----------------|
| Age (years), mean $\pm$ SD                                 | 67.3 $\pm$ 9.3             | 66.8 $\pm$ 9.0             | 0.914          |
| Male, N (%)                                                | 3 (38)                     | 3 (38)                     | 1.000          |
| Body mass index (kg/m <sup>2</sup> ), median (P25-P75)     | 26.3 (24.7-28.5)           | 26.0 (24.1-27.6)           | 0.959          |
| Hypertension, N (%)                                        | 3 (38)                     | 4 (50)                     | 1.000          |
| Dyslipidemia, N (%)                                        | 7 (88)                     | 5 (63)                     | 0.569          |
| Diabetes mellitus, N (%)                                   | 0 (0)                      | 0 (0)                      | 1.000          |
| Active or former smoker, N (%)                             | 1 (13)                     | 1 (13)                     | 1.000          |
| hs-CRP (mg/L), median (P25-P75)                            | 1.22 (0.98-2.61)           | 2.16 (0.74-3.08)           | 0.590          |
| Coronary artery disease, N (%)                             | 1 (13)                     | 1 (13)                     | 1.000          |
| Epicardial fat volume (cm <sup>3</sup> ), median (P25-P75) | 43.6 (24.7-60.4)           | 139.8 (120.9-165.1)        | <0.001         |

Data are presented as frequencies (percentages) for categorical variables. Continuous variables are presented as mean  $\pm$  standard deviation (SD) or median (P25-P75). Differences between groups were analyzed using Student's t test, Mann-Whitney U test or Fisher's exact test.

**Supplemental Table S2. Plasma microRNA screening.**

| microRNA        | Tertile 1 |               | Tertile 3 |               | P-value | Median Cq | Min Cq | Max Cq |
|-----------------|-----------|---------------|-----------|---------------|---------|-----------|--------|--------|
| hsa-let-7a-5p   | 14.85     | (14.41-15.07) | 15.71     | (14.99-16.58) | 0.105   | 25.2      | 23.4   | 26.3   |
| hsa-let-7b-3p   | 8.17      | (8.1-8.93)    | 8.87      | (8.37-9.56)   | 0.105   | 31.9      | 30.2   | 32.5   |
| hsa-let-7b-5p   | 14.54     | (14-14.92)    | 15.48     | (15.04-16.37) | 0.050   | 25.2      | 24.1   | 26.8   |
| hsa-let-7c-5p   | 10.58     | (9.65-10.83)  | 11.31     | (10.26-12.53) | 0.161   | 29.5      | 27.7   | 30.8   |
| hsa-let-7d-3p   | 13.49     | (13.25-13.94) | 14.29     | (13.76-15.28) | 0.050   | 26.5      | 24.8   | 27.3   |
| hsa-let-7d-5p   | 11.86     | (11.31-12.05) | 12.78     | (11.7-13.92)  | 0.105   | 28.2      | 25.8   | 29.6   |
| hsa-let-7e-5p   | 10.00     | (9.21-10.72)  | 11.17     | (10.03-12.12) | 0.161   | 30.0      | 28.0   | 31.4   |
| hsa-let-7f-5p   | 12.99     | (12.41-13.32) | 14.02     | (13.33-15.18) | 0.050   | 26.9      | 24.7   | 28.2   |
| hsa-let-7g-5p   | 14.40     | (13.55-14.69) | 15.28     | (14.57-16.38) | 0.065   | 25.7      | 23.6   | 26.9   |
| hsa-let-7i-5p   | 13.21     | (13.14-13.57) | 13.89     | (13.83-14.59) | 0.050   | 26.8      | 25.5   | 27.6   |
| hsa-miR-1       | 8.07      | (7.13-9)      | 9.48      | (7.74-10.48)  | 0.279   | 31.8      | 28.4   | 34.9   |
| hsa-miR-100-5p  | 8.58      | (7.35-9.29)   | 8.83      | (8.55-9.12)   | 0.574   | 31.8      | 30.3   | 33.5   |
| hsa-miR-101-3p  | 14.74     | (14.15-15.06) | 15.26     | (14.96-15.88) | 0.083   | 25.4      | 23.6   | 26.3   |
| hsa-miR-103a-3p | 15.31     | (14.41-15.43) | 16.19     | (15.2-17.46)  | 0.105   | 24.9      | 22.3   | 26.4   |
| hsa-miR-106a-5p | 16.57     | (15.87-16.79) | 17.26     | (16.99-18.13) | 0.021   | 23.5      | 21.9   | 24.4   |
| hsa-miR-106b-3p | 9.31      | (9.19-9.6)    | 10.47     | (9.44-11.28)  | 0.083   | 30.9      | 29.0   | 32.2   |
| hsa-miR-106b-5p | 13.06     | (12.64-13.55) | 14.14     | (13.21-14.69) | 0.195   | 27.0      | 25.4   | 28.2   |
| hsa-miR-107     | 12.89     | (12.29-13.2)  | 13.75     | (12.92-15.1)  | 0.105   | 27.2      | 24.8   | 28.3   |
| hsa-miR-10b-5p  | 10.81     | (9.81-11.14)  | 10.97     | (10.39-11.62) | 0.442   | 29.5      | 28.1   | 30.9   |
| hsa-miR-122-5p  | 12.83     | (12.18-13.91) | 13.57     | (11.88-14.99) | 0.574   | 27.2      | 22.7   | 30.1   |
| hsa-miR-125a-5p | 11.41     | (10.6-12.19)  | 12.26     | (11.34-13.72) | 0.234   | 28.7      | 26.5   | 30.4   |
| hsa-miR-125b-5p | 11.91     | (10.3-12.52)  | 12.77     | (12.09-13.37) | 0.105   | 28.2      | 26.6   | 30.4   |
| hsa-miR-1260a   | 10.04     | (9.73-10.57)  | 10.54     | (10.3-11.02)  | 0.130   | 30.1      | 29.2   | 31.3   |
| hsa-miR-126-3p  | 17.13     | (16.44-17.34) | 18.03     | (17.19-19.25) | 0.065   | 22.9      | 21.1   | 24.0   |
| hsa-miR-126-5p  | 13.53     | (13.03-13.96) | 14.30     | (13.98-15.59) | 0.021   | 26.3      | 24.5   | 27.4   |
| hsa-miR-127-3p  | 8.81      | (7.34-9.56)   | 9.58      | (7.42-10.63)  | 0.442   | 31.4      | 28.2   | 34.2   |
| hsa-miR-128-3p  | 9.92      | (9.75-10.04)  | 10.42     | (9.91-11.25)  | 0.195   | 30.3      | 28.5   | 30.8   |
| hsa-miR-130a-3p | 11.19     | (10.67-11.59) | 11.98     | (11.8-12.95)  | 0.015   | 28.7      | 27.0   | 29.9   |
| hsa-miR-130b-3p | 8.66      | (8.53-8.95)   | 9.49      | (9.19-10.35)  | 0.015   | 31.2      | 29.3   | 32.2   |
| hsa-miR-132-3p  | 10.01     | (9.54-10.2)   | 10.48     | (10.09-11.16) | 0.083   | 30.1      | 28.8   | 31.3   |
| hsa-miR-133a-3p | 8.44      | (8.21-9.36)   | 9.49      | (8.13-10.89)  | 0.279   | 31.6      | 28.3   | 34.5   |
| hsa-miR-133b    | 9.24      | (7.95-9.85)   | 10.35     | (9.57-11.82)  | 0.083   | 30.7      | 27.8   | 33.9   |
| hsa-miR-136-3p  | 7.95      | (7.04-9.63)   | 8.62      | (6.63-10.38)  | 0.955   | 32.6      | 22.6   | 34.0   |
| hsa-miR-136-5p  | 7.36      | (7.03-7.83)   | 6.86      | (5.29-8.97)   | 0.721   | 33.1      | 29.9   | 35.0   |
| hsa-miR-139-5p  | 11.17     | (10.48-11.94) | 12.18     | (10.07-13.27) | 0.442   | 28.9      | 27.1   | 30.7   |
| hsa-miR-140-3p  | 14.27     | (13.6-14.57)  | 14.60     | (13.9-15.27)  | 0.328   | 26.0      | 24.7   | 27.0   |
| hsa-miR-140-5p  | 11.46     | (10.99-11.77) | 12.14     | (11.84-13.32) | 0.021   | 28.7      | 26.9   | 29.8   |
| hsa-miR-141-3p  | 7.68      | (6.8-8.31)    | 8.24      | (7.81-9.25)   | 0.279   | 32.2      | 30.9   | 35.0   |
| hsa-miR-142-3p  | 15.30     | (14.57-15.57) | 16.19     | (15.22-16.99) | 0.161   | 24.9      | 22.5   | 26.4   |
| hsa-miR-142-5p  | 12.09     | (11.94-12.35) | 13.05     | (12.53-14.02) | 0.015   | 27.9      | 25.5   | 28.7   |
| hsa-miR-143-3p  | 12.46     | (10.87-13.17) | 12.67     | (12.28-13.7)  | 0.574   | 27.6      | 25.1   | 29.4   |
| hsa-miR-144-3p  | 13.50     | (12.96-14.07) | 13.61     | (13.21-14.12) | 0.798   | 26.9      | 25.2   | 27.8   |
| hsa-miR-144-5p  | 10.03     | (9.4-10.64)   | 10.19     | (10-10.28)    | 0.645   | 30.3      | 29.2   | 31.1   |
| hsa-miR-145-5p  | 11.54     | (10.85-12.41) | 12.51     | (11.84-13.97) | 0.083   | 28.0      | 25.8   | 29.7   |

|                        |              |                      |              |                      |              |             |             |             |
|------------------------|--------------|----------------------|--------------|----------------------|--------------|-------------|-------------|-------------|
| <b>hsa-miR-146a-5p</b> | <b>14.08</b> | <b>(13.71-14.44)</b> | <b>15.08</b> | <b>(14.65-16.11)</b> | <b>0.010</b> | <b>25.7</b> | <b>24.0</b> | <b>26.7</b> |
| hsa-miR-146b-5p        | 8.40         | (7.37-9.16)          | 9.18         | (8.9-10.64)          | 0.083        | 31.3        | 29.6        | 33.1        |
| <b>hsa-miR-148a-3p</b> | <b>12.11</b> | <b>(11.86-12.57)</b> | <b>12.72</b> | <b>(12.54-13.16)</b> | <b>0.065</b> | <b>27.9</b> | <b>26.1</b> | <b>29.1</b> |
| <b>hsa-miR-148b-3p</b> | <b>13.09</b> | <b>(12.9-13.37)</b>  | <b>13.91</b> | <b>(13.65-14.64)</b> | <b>0.010</b> | <b>26.8</b> | <b>24.4</b> | <b>27.5</b> |
| hsa-miR-150-5p         | 14.04        | (13.29-14.19)        | 14.10        | (13.78-14.86)        | 0.505        | 26.2        | 25.5        | 27.3        |
| hsa-miR-151a-3p        | 11.91        | (11.46-12.26)        | 12.85        | (12.37-14.14)        | 0.015        | 27.9        | 26.1        | 29.1        |
| hsa-miR-151a-5p        | 13.98        | (13.69-14.55)        | 15.01        | (14.27-16.08)        | 0.038        | 25.8        | 24.0        | 26.9        |
| <b>hsa-miR-152-3p</b>  | <b>11.58</b> | <b>(10.49-12)</b>    | <b>12.59</b> | <b>(12.03-12.96)</b> | <b>0.028</b> | <b>28.3</b> | <b>26.7</b> | <b>29.9</b> |
| hsa-miR-154-5p         | 10.39        | (9.66-10.94)         | 10.57        | (8.9-11.71)          | 0.798        | 30.0        | 27.7        | 33.3        |
| hsa-miR-155-5p         | 8.54         | (7.92-9.1)           | 9.60         | (8.68-10.73)         | 0.105        | 31.2        | 29.3        | 33.4        |
| hsa-miR-15a-5p         | 16.02        | (15.78-16.52)        | 16.31        | (16.21-17.26)        | 0.083        | 24.2        | 22.8        | 24.7        |
| <b>hsa-miR-15b-3p</b>  | <b>11.67</b> | <b>(11.54-11.72)</b> | <b>12.31</b> | <b>(11.92-12.98)</b> | <b>0.010</b> | <b>28.5</b> | <b>27.2</b> | <b>29.1</b> |
| <b>hsa-miR-15b-5p</b>  | <b>12.36</b> | <b>(12.12-12.67)</b> | <b>13.25</b> | <b>(13.06-14.55)</b> | <b>0.007</b> | <b>27.4</b> | <b>25.4</b> | <b>28.6</b> |
| hsa-miR-16-2-3p        | 10.77        | (10.17-11.41)        | 11.10        | (10.65-11.59)        | 0.382        | 29.5        | 28.4        | 30.3        |
| hsa-miR-16-5p          | 21.25        | (20.48-21.52)        | 21.57        | (21.09-22.16)        | 0.130        | 18.9        | 17.8        | 19.9        |
| hsa-miR-17-5p          | 10.05        | (9.36-10.37)         | 10.81        | (10.51-11.74)        | 0.021        | 29.8        | 28.5        | 31.0        |
| hsa-miR-181a-5p        | 11.69        | (11.02-12.67)        | 12.96        | (12.07-13.64)        | 0.234        | 27.9        | 26.1        | 29.6        |
| hsa-miR-185-5p         | 16.67        | (16.51-17.03)        | 17.35        | (17.12-18.22)        | 0.038        | 23.4        | 22.2        | 24.1        |
| hsa-miR-186-5p         | 8.98         | (8.59-9.54)          | 9.92         | (9.47-10.7)          | 0.050        | 30.9        | 29.4        | 32.3        |
| hsa-miR-18a-5p         | 13.28        | (12.55-13.5)         | 13.90        | (13.77-15.71)        | 0.040        | 26.8        | 24.8        | 28.2        |
| hsa-miR-18b-5p         | 13.01        | (12.21-13.25)        | 13.66        | (13.34-14.95)        | 0.028        | 27.0        | 25.2        | 28.4        |
| hsa-miR-191-5p         | 14.62        | (13.74-15.06)        | 15.42        | (14.95-17.09)        | 0.038        | 25.3        | 23.3        | 26.8        |
| hsa-miR-192-5p         | 11.92        | (10.99-12.74)        | 12.35        | (11.73-12.8)         | 0.574        | 28.3        | 25.7        | 29.5        |
| hsa-miR-193a-5p        | 7.31         | (5.92-7.75)          | 7.28         | (7.01-7.83)          | 0.721        | 33.1        | 31.4        | 34.9        |
| hsa-miR-194-5p         | 10.01        | (9.27-10.56)         | 10.49        | (10.04-10.98)        | 0.279        | 30.1        | 28.1        | 31.4        |
| hsa-miR-195-5p         | 8.67         | (8.55-9.72)          | 9.88         | (8.75-10.21)         | 0.195        | 30.9        | 29.7        | 32.5        |
| hsa-miR-197-3p         | 12.07        | (11.52-12.46)        | 12.75        | (12.14-13.89)        | 0.083        | 27.8        | 26.3        | 29.2        |
| hsa-miR-199a-3p        | 13.54        | (13.01-13.95)        | 14.43        | (13.78-15.17)        | 0.083        | 26.5        | 24.2        | 27.3        |
| hsa-miR-199a-5p        | 11.27        | (10.52-11.52)        | 12.27        | (11.2-13.18)         | 0.161        | 28.8        | 26.2        | 30.0        |
| hsa-miR-19a-3p         | 16.89        | (16.62-17.23)        | 17.46        | (17.13-18.14)        | 0.083        | 23.3        | 21.5        | 24.0        |
| hsa-miR-19b-3p         | 18.10        | (17.7-18.58)         | 18.74        | (18.37-19.36)        | 0.083        | 22.1        | 20.6        | 22.7        |
| hsa-miR-200a-3p        | 5.31         | (5.06-5.82)          | 6.33         | (5.85-7.21)          | 0.015        | 34.6        | 32.2        | 35.0        |
| hsa-miR-200c-3p        | 7.88         | (7.32-8.38)          | 8.87         | (7.9-10.15)          | 0.083        | 32.0        | 30.1        | 33.1        |
| hsa-miR-205-5p         | 6.07         | (5.21-6.72)          | 6.13         | (5.23-6.96)          | 0.798        | 34.0        | 32.8        | 35.0        |
| hsa-miR-20a-5p         | 16.66        | (16.17-16.97)        | 17.43        | (17.13-18.26)        | 0.021        | 23.3        | 22.0        | 24.2        |
| hsa-miR-20b-5p         | 7.56         | (7.33-8.15)          | 8.17         | (7.36-8.35)          | 0.382        | 32.5        | 31.6        | 34.1        |
| hsa-miR-210-3p         | 10.35        | (9.83-10.8)          | 11.33        | (10.68-11.41)        | 0.065        | 29.7        | 28.7        | 30.5        |
| hsa-miR-2110           | 7.81         | (7.27-8.19)          | 8.84         | (8.48-9.46)          | 0.028        | 32.1        | 31.1        | 33.3        |
| hsa-miR-215-5p         | 10.67        | (9.78-11.5)          | 11.30        | (10.52-11.81)        | 0.279        | 29.4        | 26.6        | 31.2        |
| <b>hsa-miR-21-5p</b>   | <b>17.16</b> | <b>(16.66-17.58)</b> | <b>17.87</b> | <b>(17.68-18.77)</b> | <b>0.015</b> | <b>22.7</b> | <b>21.0</b> | <b>24.9</b> |
| hsa-miR-221-3p         | 15.55        | (15.34-15.76)        | 16.49        | (15.83-17.45)        | 0.038        | 24.4        | 22.6        | 25.7        |
| hsa-miR-222-3p         | 13.72        | (13.26-14.06)        | 14.35        | (14.18-14.9)         | 0.038        | 26.2        | 25.3        | 27.3        |
| hsa-miR-223-3p         | 19.39        | (18.83-19.54)        | 20.23        | (19.52-21.45)        | 0.050        | 20.7        | 18.8        | 22.0        |
| hsa-miR-223-5p         | 8.73         | (8.49-9.04)          | 9.43         | (8.62-10.57)         | 0.161        | 31.3        | 29.6        | 32.1        |
| <b>hsa-miR-22-3p</b>   | <b>13.46</b> | <b>(13.18-13.5)</b>  | <b>14.07</b> | <b>(13.73-14.58)</b> | <b>0.010</b> | <b>26.7</b> | <b>25.0</b> | <b>27.4</b> |
| hsa-miR-22-5p          | 9.39         | (9.04-10.02)         | 9.75         | (9.44-10.55)         | 0.442        | 30.8        | 29.1        | 32.0        |
| hsa-miR-23a-3p         | 17.41        | (16.7-17.66)         | 18.21        | (17.68-19.42)        | 0.050        | 22.6        | 20.7        | 23.6        |
| hsa-miR-23b-3p         | 15.18        | (14.62-15.51)        | 16.18        | (15.58-17.5)         | 0.028        | 24.7        | 22.7        | 25.8        |

|                       |              |                      |              |                      |              |             |             |             |
|-----------------------|--------------|----------------------|--------------|----------------------|--------------|-------------|-------------|-------------|
| hsa-miR-24-3p         | 16.96        | (16.73-17.44)        | 18.09        | (17.45-18.84)        | 0.021        | 22.8        | 21.3        | 23.8        |
| hsa-miR-25-3p         | 16.44        | (16-16.93)           | 16.78        | (16.58-17.69)        | 0.105        | 23.8        | 22.3        | 24.5        |
| hsa-miR-26a-5p        | 13.12        | (12.18-13.67)        | 14.18        | (13.13-15.79)        | 0.105        | 26.8        | 24.4        | 28.3        |
| hsa-miR-26b-5p        | 11.67        | (10.87-12.32)        | 12.79        | (12.42-14.26)        | 0.050        | 27.9        | 25.8        | 29.9        |
| <b>hsa-miR-27a-3p</b> | <b>13.38</b> | <b>(12.97-13.73)</b> | <b>14.36</b> | <b>(14-15.59)</b>    | <b>0.028</b> | <b>26.4</b> | <b>23.9</b> | <b>27.5</b> |
| <b>hsa-miR-27b-3p</b> | <b>15.23</b> | <b>(14.57-15.48)</b> | <b>16.08</b> | <b>(15.73-17.25)</b> | <b>0.010</b> | <b>24.6</b> | <b>22.6</b> | <b>25.7</b> |
| hsa-miR-28-3p         | 10.91        | (9.76-11.04)         | 11.64        | (11.21-12.96)        | 0.028        | 29.1        | 27.3        | 31.0        |
| hsa-miR-28-5p         | 10.98        | (9.74-11.22)         | 11.93        | (11.15-13.17)        | 0.083        | 29.1        | 26.8        | 30.9        |
| hsa-miR-29a-3p        | 11.47        | (10.83-11.96)        | 11.67        | (11.44-12.32)        | 0.505        | 28.7        | 27.6        | 30.0        |
| hsa-miR-29b-3p        | 10.62        | (10.06-10.91)        | 11.24        | (10.65-11.77)        | 0.234        | 29.5        | 27.4        | 30.4        |
| hsa-miR-29c-3p        | 11.80        | (11-11.92)           | 12.24        | (12.05-12.87)        | 0.050        | 28.4        | 26.8        | 29.5        |
| hsa-miR-301a-3p       | 11.19        | (10.7-11.62)         | 12.33        | (11.79-13.74)        | 0.028        | 28.5        | 26.5        | 30.8        |
| hsa-miR-30a-5p        | 10.13        | (9.34-10.57)         | 10.78        | (10.62-11.29)        | 0.065        | 29.9        | 29.0        | 31.3        |
| hsa-miR-30b-5p        | 13.37        | (12.57-13.94)        | 14.30        | (13.24-15.65)        | 0.065        | 26.6        | 24.1        | 28.2        |
| hsa-miR-30c-5p        | 13.03        | (12.5-13.54)         | 14.01        | (13.27-14.92)        | 0.065        | 26.9        | 25.1        | 27.8        |
| hsa-miR-30d-5p        | 15.21        | (14.68-15.5)         | 16.10        | (15.82-17.33)        | 0.015        | 24.6        | 23.0        | 25.8        |
| hsa-miR-30e-3p        | 8.66         | (7.8-9.14)           | 9.42         | (9.08-10.78)         | 0.065        | 31.1        | 29.4        | 32.7        |
| hsa-miR-30e-5p        | 14.74        | (14.45-15.08)        | 15.42        | (15.06-16.44)        | 0.038        | 25.3        | 23.9        | 26.1        |
| hsa-miR-320a          | 15.54        | (15.05-15.83)        | 16.00        | (15.73-16.52)        | 0.050        | 24.6        | 23.8        | 25.6        |
| hsa-miR-320b          | 13.24        | (12.76-13.6)         | 13.95        | (13.65-14.38)        | 0.015        | 26.9        | 25.7        | 27.7        |
| hsa-miR-320c          | 12.26        | (11.83-12.55)        | 12.75        | (12.4-13.28)         | 0.028        | 27.9        | 26.8        | 28.6        |
| hsa-miR-320d          | 11.02        | (10.54-11.47)        | 11.35        | (11.09-12.04)        | 0.161        | 29.2        | 28.2        | 30.0        |
| hsa-miR-324-3p        | 10.82        | (10.25-11.17)        | 11.64        | (11.46-12.1)         | 0.083        | 29.2        | 27.8        | 30.6        |
| hsa-miR-324-5p        | 11.54        | (10.81-11.61)        | 12.37        | (11.8-13.28)         | 0.038        | 28.5        | 26.7        | 30.1        |
| hsa-miR-32-5p         | 9.44         | (9.09-9.87)          | 9.79         | (9.6-10.01)          | 0.382        | 30.8        | 28.8        | 31.7        |
| hsa-miR-326           | 8.00         | (7.25-9.03)          | 8.83         | (8.39-10.16)         | 0.130        | 31.9        | 28.9        | 33.2        |
| hsa-miR-328-3p        | 11.71        | (11.12-12.12)        | 12.82        | (12.03-13.81)        | 0.038        | 28.2        | 26.4        | 29.4        |
| hsa-miR-331-3p        | 10.56        | (9.96-10.98)         | 11.76        | (10.9-13.03)         | 0.050        | 29.3        | 27.2        | 30.5        |
| hsa-miR-335-3p        | 9.02         | (8.55-9.47)          | 10.15        | (8.92-10.63)         | 0.195        | 31.0        | 28.3        | 32.6        |
| hsa-miR-335-5p        | 8.51         | (7.9-8.84)           | 9.60         | (8.91-10.5)          | 0.021        | 31.4        | 28.7        | 33.0        |
| hsa-miR-338-3p        | 10.16        | (9.71-10.59)         | 11.19        | (10.36-12.24)        | 0.050        | 29.9        | 27.7        | 31.2        |
| <b>hsa-miR-339-3p</b> | <b>10.04</b> | <b>(9.64-10.08)</b>  | <b>10.71</b> | <b>(10.38-11.96)</b> | <b>0.007</b> | <b>30.0</b> | <b>28.1</b> | <b>30.9</b> |
| hsa-miR-339-5p        | 11.39        | (10.61-11.63)        | 12.05        | (11.5-13.72)         | 0.050        | 28.7        | 26.3        | 29.7        |
| hsa-miR-33a-5p        | 7.51         | (7.14-8.77)          | 8.48         | (7.44-9.55)          | 0.234        | 32.3        | 29.3        | 34.5        |
| hsa-miR-342-3p        | 11.68        | (10.83-12.13)        | 11.80        | (11.1-12.8)          | 0.645        | 28.7        | 27.6        | 30.3        |
| hsa-miR-34a-5p        | 9.00         | (8.57-9.26)          | 8.76         | (7.96-9.44)          | 0.574        | 31.5        | 30.6        | 33.3        |
| hsa-miR-361-5p        | 12.79        | (12.56-13.27)        | 13.56        | (13.32-14.68)        | 0.021        | 27.0        | 25.6        | 27.9        |
| hsa-miR-362-3p        | 8.48         | (8.04-8.71)          | 9.17         | (8.79-9.55)          | 0.050        | 31.7        | 30.0        | 32.4        |
| hsa-miR-363-3p        | 12.26        | (11.8-12.58)         | 12.30        | (11.93-12.72)        | 0.798        | 28.1        | 27.3        | 29.3        |
| hsa-miR-365a-3p       | 7.62         | (6.36-8.66)          | 8.29         | (7.09-9.07)          | 0.574        | 32.4        | 30.0        | 35.0        |
| hsa-miR-374a-5p       | 9.40         | (8.8-10.1)           | 10.54        | (9.76-12.24)         | 0.038        | 30.3        | 27.8        | 31.7        |
| hsa-miR-374b-5p       | 11.41        | (10.5-11.83)         | 12.37        | (11.58-14.02)        | 0.083        | 28.5        | 25.9        | 30.5        |
| hsa-miR-375           | 8.47         | (7.87-8.72)          | 9.03         | (8.7-10.19)          | 0.021        | 31.7        | 29.9        | 34.6        |
| hsa-miR-376a-3p       | 9.92         | (9.39-10.08)         | 10.00        | (8.41-11.2)          | 0.798        | 30.4        | 27.7        | 33.7        |
| hsa-miR-376c-3p       | 11.89        | (11.26-12.12)        | 12.03        | (10.34-13.31)        | 0.645        | 28.4        | 25.8        | 32.5        |
| hsa-miR-382-5p        | 10.87        | (10.23-11.09)        | 11.29        | (9.76-12.58)         | 0.234        | 29.3        | 27.1        | 32.1        |
| hsa-miR-409-3p        | 11.06        | (10.19-11.37)        | 11.47        | (9.35-12.72)         | 0.382        | 29.3        | 26.6        | 32.8        |
| hsa-miR-421           | 9.39         | (8.94-10.01)         | 10.35        | (10-11.55)           | 0.028        | 30.4        | 28.5        | 31.7        |

|                       |              |                      |              |                     |              |             |             |             |
|-----------------------|--------------|----------------------|--------------|---------------------|--------------|-------------|-------------|-------------|
| hsa-miR-423-3p        | 12.65        | (12.08-12.98)        | 13.61        | (12.97-14.7)        | 0.050        | 27.3        | 25.3        | 28.4        |
| hsa-miR-423-5p        | 13.33        | (13.12-13.77)        | 13.78        | (13.7-14.6)         | 0.083        | 26.7        | 25.6        | 27.2        |
| hsa-miR-424-5p        | 11.04        | (10.39-11.46)        | 11.03        | (9.87-11.63)        | 0.878        | 29.4        | 27.5        | 31.4        |
| hsa-miR-425-3p        | 10.49        | (10.06-10.82)        | 11.34        | (10.93-12.48)       | 0.021        | 29.3        | 27.6        | 30.4        |
| hsa-miR-425-5p        | 14.02        | (13.61-14.48)        | 14.62        | (14.43-15.37)       | 0.105        | 26.2        | 24.7        | 26.8        |
| hsa-miR-451a          | 21.29        | (20.38-21.64)        | 21.24        | (20.72-21.77)       | 0.645        | 19.2        | 17.7        | 20.5        |
| hsa-miR-454-3p        | 8.89         | (8.19-9.28)          | 10.07        | (9.44-11.17)        | 0.015        | 30.8        | 29.2        | 32.8        |
| hsa-miR-483-5p        | 7.00         | (6.75-7.49)          | 7.54         | (7.08-7.95)         | 0.234        | 33.0        | 31.7        | 35.0        |
| hsa-miR-484           | 12.69        | (12.33-13)           | 13.32        | (13.25-14.37)       | 0.028        | 27.4        | 25.7        | 28.0        |
| hsa-miR-485-3p        | 9.44         | (8.81-10.06)         | 10.01        | (7.13-10.9)         | 0.721        | 31.0        | 28.1        | 34.4        |
| hsa-miR-486-5p        | 16.65        | (16.12-17.04)        | 16.94        | (16.35-17.49)       | 0.382        | 23.6        | 22.2        | 24.3        |
| hsa-miR-495-3p        | 9.57         | (9.05-10.32)         | 9.59         | (7.74-10.74)        | 0.959        | 30.6        | 28.2        | 33.4        |
| hsa-miR-497-5p        | 7.75         | (7.4-8.23)           | 7.63         | (7.26-7.74)         | 0.505        | 32.7        | 30.4        | 33.3        |
| hsa-miR-501-3p        | 8.20         | (7.95-8.93)          | 8.63         | (8.45-8.94)         | 0.083        | 31.8        | 31.1        | 32.8        |
| hsa-miR-502-3p        | 9.09         | (8.66-9.69)          | 9.52         | (9.13-9.9)          | 0.195        | 30.9        | 30.4        | 31.9        |
| hsa-miR-505-3p        | 9.79         | (9.27-10.05)         | 10.50        | (10.17-11.24)       | 0.038        | 30.1        | 28.8        | 31.3        |
| hsa-miR-532-3p        | 9.26         | (9.1-9.73)           | 9.86         | (9.46-10.57)        | 0.161        | 30.7        | 29.7        | 31.9        |
| hsa-miR-532-5p        | 10.43        | (9.76-10.94)         | 11.00        | (10.66-11.4)        | 0.083        | 29.6        | 28.6        | 30.7        |
| hsa-miR-543           | 9.68         | (8.73-9.93)          | 10.09        | (8.35-10.86)        | 0.442        | 30.6        | 28.4        | 34.4        |
| hsa-miR-574-3p        | 10.18        | (9.33-10.71)         | 10.78        | (10.34-12.26)       | 0.105        | 29.8        | 27.9        | 31.3        |
| hsa-miR-584-5p        | 8.98         | (8.3-9.27)           | 10.02        | (9.59-10.92)        | 0.038        | 30.9        | 28.9        | 32.0        |
| <b>hsa-miR-590-5p</b> | <b>11.81</b> | <b>(11.63-11.91)</b> | <b>12.64</b> | <b>(12.4-13.61)</b> | <b>0.010</b> | <b>28.1</b> | <b>25.9</b> | <b>29.0</b> |
| hsa-miR-629-5p        | 8.79         | (8.27-9.24)          | 9.08         | (8.56-9.33)         | 0.328        | 31.3        | 30.7        | 32.2        |
| hsa-miR-652-3p        | 13.01        | (12.28-13.16)        | 13.84        | (13.19-14.91)       | 0.038        | 27.1        | 25.3        | 28.3        |
| hsa-miR-660-5p        | 12.48        | (12.02-12.7)         | 12.95        | (12.61-13.18)       | 0.130        | 27.7        | 26.9        | 28.9        |
| hsa-miR-7-1-3p        | 8.91         | (8.33-9.11)          | 9.76         | (9.31-10.73)        | 0.050        | 31.2        | 29.0        | 32.2        |
| hsa-miR-7-5p          | 8.38         | (7.24-9.08)          | 8.56         | (7.59-9.29)         | 0.505        | 31.9        | 30.1        | 33.5        |
| hsa-miR-766-3p        | 10.10        | (9.48-10.52)         | 11.18        | (10.41-12.82)       | 0.015        | 29.8        | 27.2        | 31.7        |
| hsa-miR-874-3p        | 7.06         | (6.08-7.38)          | 7.59         | (7.07-8.27)         | 0.161        | 33.1        | 31.9        | 35.0        |
| hsa-miR-877-5p        | 7.97         | (7.27-8.64)          | 8.70         | (8.54-9.5)          | 0.105        | 32.0        | 30.2        | 33.7        |
| hsa-miR-885-5p        | 7.27         | (5.37-8.83)          | 8.12         | (6.86-9.09)         | 0.279        | 32.9        | 29.4        | 35.0        |
| hsa-miR-92a-3p        | 16.66        | (16.2-17.03)         | 17.25        | (16.99-17.74)       | 0.021        | 23.4        | 22.4        | 24.1        |
| hsa-miR-92b-3p        | 6.58         | (5.87-6.98)          | 7.47         | (6.9-8.16)          | 0.028        | 33.3        | 32.0        | 34.5        |
| hsa-miR-93-3p         | 9.70         | (9.1-10.28)          | 10.54        | (10.4-11.6)         | 0.038        | 30.1        | 28.3        | 31.5        |
| hsa-miR-93-5p         | 16.14        | (15.89-16.53)        | 16.95        | (16.71-17.74)       | 0.021        | 23.9        | 22.7        | 24.4        |
| hsa-miR-99a-5p        | 10.47        | (9.48-10.83)         | 10.90        | (10.35-11.13)       | 0.105        | 29.8        | 29.1        | 31.4        |
| hsa-miR-99b-5p        | 10.37        | (9.57-11.21)         | 11.05        | (10.34-12.29)       | 0.130        | 29.5        | 28.0        | 30.8        |
| mmu-miR-378a-3p       | 11.86        | (11.33-12.14)        | 12.11        | (11.56-12.71)       | 0.328        | 28.4        | 27.4        | 29.3        |

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Data are presented as median (P25-P75). Differences between groups were analyzed using Mann-Whitney U test. Candidates in bold.

**Supplemental Table S3. MicroRNA candidates.**

|                        | MIRBase ID   | Chromosome | Start     | End       | Strand | Seed+m8  | microRNA family   |
|------------------------|--------------|------------|-----------|-----------|--------|----------|-------------------|
| <b>hsa-miR-15b-3p</b>  | MIMAT0004586 | chr3       | 160404588 | 160404685 | +      | GAAUCAU  | NA                |
| <b>hsa-miR-15b-5p</b>  | MIMAT0000417 | chr3       | 160404588 | 160404685 | +      | AGCAGCA  | NA                |
| <b>hsa-miR-21-5p</b>   | MIMAT0000076 | chr1       | 59841266  | 59841337  | +      | AGCUUUAU | miR-21-5p/590-5p  |
| <b>hsa-miR-22-3p</b>   | MIMAT0000077 | chr17      | 1713903   | 1713987   | -      | AGCUGCC  | NA                |
| <b>hsa-miR-27a-3p</b>  | MIMAT0000084 | chr19      | 13836440  | 13836517  | -      | UCACAGU  | miR-27-3p         |
| <b>hsa-miR-27b-3p</b>  | MIMAT0000419 | chr9       | 95085445  | 95085541  | +      | UCACAGU  | miR-27-3p         |
| <b>hsa-miR-146a-5p</b> | MIMAT0000449 | chr5       | 160485352 | 160485450 | +      | GAGAACU  | NA                |
| <b>hsa-miR-148a-3p</b> | MIMAT0000243 | chr7       | 25949919  | 25949986  | -      | CAGUGCA  | miR-148-3p/152-3p |
| <b>hsa-miR-148b-3p</b> | MIMAT0000759 | chr12      | 54337216  | 54337314  | +      | CAGUGCA  | miR-148-3p/152-3p |
| <b>hsa-miR-152-3p</b>  | MIMAT0000438 | chr17      | 48037161  | 48037247  | -      | CAGUGCA  | miR-148-3p/152-3p |
| <b>hsa-miR-339-3p</b>  | MIMAT0004702 | chr7       | 1022933   | 1023026   | -      | GAGCGCC  | NA                |
| <b>hsa-miR-590-5p</b>  | MIMAT0003258 | chr7       | 74191198  | 74191294  | +      | AGCUUUAU | miR-21-5p/590-5p  |

miRBase database (<http://www.mirbase.org/>) and Targetscan (<http://www.targetscan.org/>) were used to describe the microRNAs. NA: Not applicable.

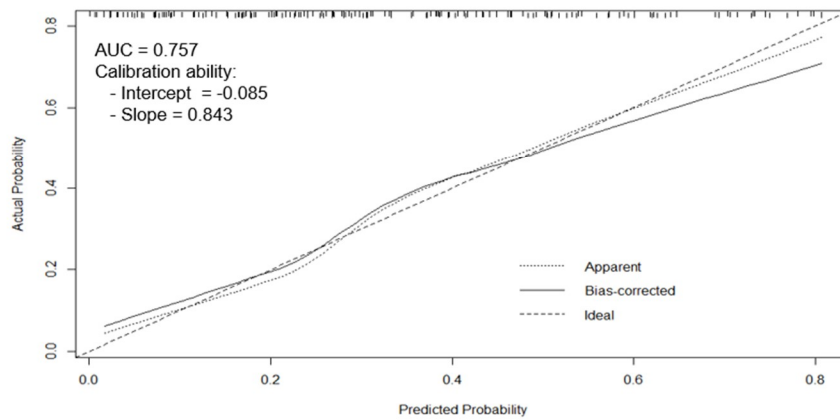
Supplemental Table S4. Correlations between epicardial fat volume and plasma microRNAs.

|     |                | miR-15b-3p | miR-15b-5p | miR-21-5p | miR-22-3p | miR-27a-3p | miR-27b-3p | miR-146a-5p | miR-148a-3p | miR-148b-3p | miR-152-3p | miR-339-3p | miR-590-5p |
|-----|----------------|------------|------------|-----------|-----------|------------|------------|-------------|-------------|-------------|------------|------------|------------|
| EFV | Spearman's rho | 0.192      | 0.086      | 0.054     | 0.165     | 0.076      | 0.125      | 0.034       | 0.171       | 0.160       | 0.130      | 0.127      | 0.141      |
|     | P-value        | 0.010      | 0.251      | 0.470     | 0.027     | 0.308      | 0.095      | 0.647       | 0.022       | 0.032       | 0.082      | 0.090      | 0.059      |

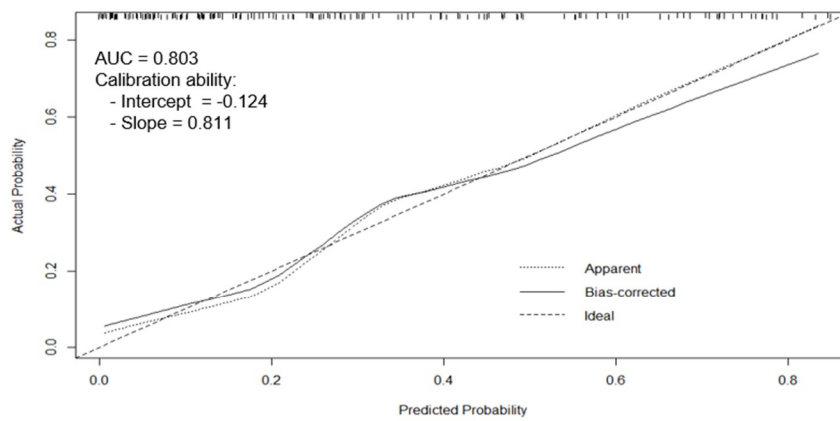
EFV: Epicardial fat volume

# SUPPLEMENTAL FIGURE S1

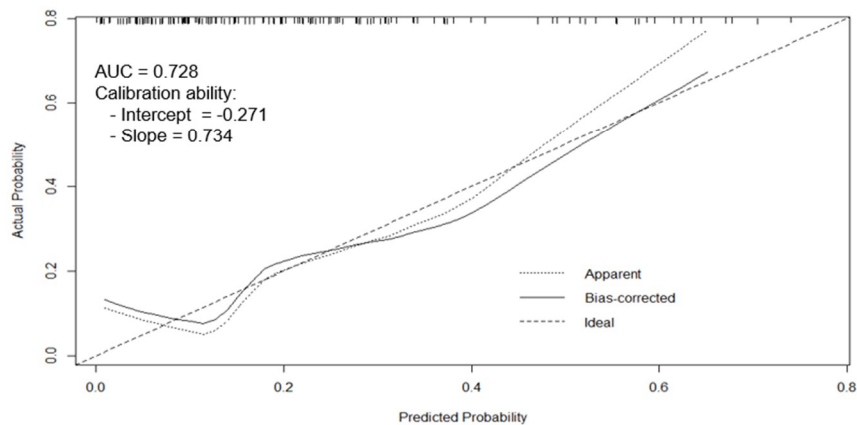
**A**



**B**



**C**



**Supplemental Figure S1. Calibration plots (with internal validation).** Calibration of the plasma microRNA models for epicardial fat volume tertiles (A), the cutoff proposed by Spearman et al. [15] (B) and the cutoff proposed by Shmilovich et al. [21] (C).

**A**

Area under the ROC curve of plasma microRNAs.

|                          | AUC   | 95% CI        | P-value |
|--------------------------|-------|---------------|---------|
| miR-15b-3p               | 0.615 | (0.508-0.722) | 0.040   |
| miR-15b-5p               | 0.535 | (0.418-0.653) | 0.529   |
| miR-21-5p                | 0.522 | (0.408-0.636) | 0.697   |
| miR-22-3p                | 0.599 | (0.486-0.712) | 0.077   |
| miR-27a-3p               | 0.526 | (0.401-0.651) | 0.643   |
| miR-27b-3p               | 0.548 | (0.421-0.675) | 0.388   |
| miR-146a-5p              | 0.519 | (0.398-0.639) | 0.737   |
| miR-148a-3p              | 0.597 | (0.487-0.707) | 0.082   |
| miR-148b-3p              | 0.575 | (0.454-0.697) | 0.179   |
| miR-152-3p               | 0.583 | (0.465-0.701) | 0.139   |
| miR-339-3p               | 0.548 | (0.427-0.669) | 0.390   |
| miR-590-5p               | 0.580 | (0.465-0.695) | 0.153   |
| miR-15b pair             | 0.634 | (0.526-0.742) | 0.017   |
| miR-21-5p/590-5p family  | 0.568 | (0.455-0.687) | 0.226   |
| miR-27-3p family         | 0.600 | (0.489-0.712) | 0.073   |
| miR-148-3p/152-3p family | 0.588 | (0.478-0.697) | 0.118   |

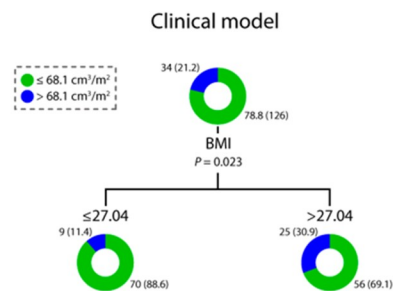
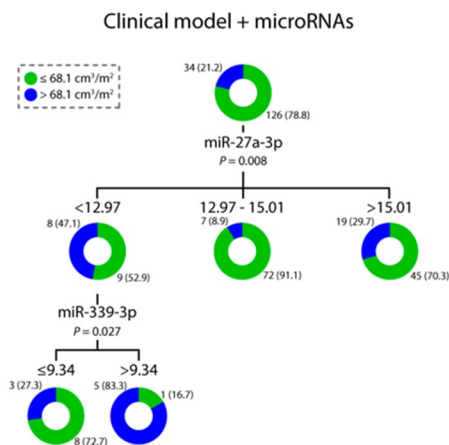
AUC: Area Under the ROC curve; 95% CI: 95% confidence interval.

**B**

Performance of plasma microRNAs as biomarkers.

|                                   | OR (95% CI)          | P-value | AUC (95% CI)        | P-value (vs CM) | IDI (95% CI)        | P-value | NRI (95% CI)        | P-value |
|-----------------------------------|----------------------|---------|---------------------|-----------------|---------------------|---------|---------------------|---------|
| <b>Clinical model</b>             |                      |         | 0.669 (0.576-0.762) |                 |                     |         |                     |         |
| Age                               | 1.025 (0.992-1.063)  | 0.152   |                     |                 |                     |         |                     |         |
| Sex                               | 1.490 (0.670-3.472)  | 0.338   |                     |                 |                     |         |                     |         |
| BMI                               | 1.060 (0.973-1.156)  | 0.180   |                     |                 |                     |         |                     |         |
| Diabetes mellitus                 | 1.748 (0.688-4.270)  | 0.227   |                     |                 |                     |         |                     |         |
| <b>Clinical model + microRNAs</b> |                      |         | 0.783 (0.685-0.882) | 0.025           | 0.163 (0.094-0.232) | <0.001  | 0.745 (0.397-10.93) | <0.001  |
| Age                               | 1.023 (0.986-1.064)  | 0.247   |                     |                 |                     |         |                     |         |
| Sex                               | 1.987 (0.826-5.085)  | 0.136   |                     |                 |                     |         |                     |         |
| BMI                               | 1.070 (0.975-1.175)  | 0.150   |                     |                 |                     |         |                     |         |
| Diabetes mellitus                 | 1.418 (0.499-3.834)  | 0.499   |                     |                 |                     |         |                     |         |
| miR-27a-3p                        | 0.179 (0.046-0.623)  | 0.010   |                     |                 |                     |         |                     |         |
| miR-146a-5p                       | 0.338 (0.126-0.853)  | 0.025   |                     |                 |                     |         |                     |         |
| miR-148b-3p                       | 3.790 (1.245-14.193) | 0.034   |                     |                 |                     |         |                     |         |
| miR-152-3p                        | 0.179 (0.046-0.623)  | 0.010   |                     |                 |                     |         |                     |         |

Variables included in the clinical model: Age, sex, body mass index and diabetes mellitus. CM: Clinical model; OR: Odds ratio; 95% CI: 95% confidence interval. AUC: Area Under the ROC curve; IDI: Integrated discrimination improvement; NRI: Net reclassification improvement.

**C****D**

**Supplemental Figure S2. Plasma microRNAs (miRNAs) as biomarkers of epicardial fat volume-indexed (EFVi), according to the cutoff proposed by Shmilovich et al. [21].** **A)** Area under the ROC curve for each individual miRNAs and for combinations of miRNAs in pairs or families. **B)** Performance of plasma miRNAs as biomarkers. **C-D)** Decision trees calculated by Chi-squared Automatic Interaction Detector (CHAID) algorithm. The following variables were included in the clinical model: age, sex, body mass index and diabetes mellitus. MicroRNA levels were log<sub>2</sub>-transformed. For logistic regression models, data are presented as an odds ratio (OR) and 95% confidence intervals (CI). For discrimination analysis, data are presented as the AUC and 95% CI. For reclassification analysis, data are presented as the Integrated

Discrimination Improvement (IDI) index and Net Reclassification Improvement (NRI) index and their respective 95% CI. For decision trees, data are shown as frequency (percentage) of patients in each study group.