Subclinical Myocardial Injury and Risk of COVID-19 in the General Population: The Trøndelag Health Study

To the Editor:

Cardiovascular disease (CVD) is a risk factor for a severe clinical course in COVID-19 (1), and CVD risk factors associate with the risk of contracting COVID-19 in the general population (2). Subclinical myocardial injury, quantified by cardiac troponin, is common in patients hospitalized with COVID-19 (3), but its association with risk of COVID-19 is unknown. We hypothesized that subclinical myocardial injury is associated with incident COVID-19 in the general population.

The Trøndelag Health (HUNT) Study is the largest population-based cohort in Norway (4), and the fourth study visit (HUNT4) was conducted from 2017 to 2019 including 56,078 participants. The study was approved by the ethics committee and all participants provided informed written consent.

For the current investigation, we included all study participants from HUNT4 with measurement of high-sensitivity cardiac troponin I (cTnI, ARCHITECT STAT High Sensitive Troponin, assay 99th percentile 16 ng/L for women and 34 ng/L for men). cTnI analysis was performed within 24 h of serum collection. Information on incident COVID-19 was acquired from the Norwegian Surveillance Service for Communicable Diseases and all-cause mortality from the Norwegian Cause of Death Registry. Clinical end points were obtained through May 31, 2021. We used a Fine and Gray proportional subhazards model to analyze associations with incident COVID-19, using all-cause mortality as competing risk. We adjusted for age, sex, and established risk factors of severe COVID-19 (i.e., CVD, diabetes mellitus, body mass index, and current smoking) (1). Prognostic accuracy was assessed by c statistics and the net reclassification index (NRI).

cTnI was measured in 37,835 study participants from HUNT4. During a median follow-up time of 1083 (interquartile range 943 to 1152) days, 237 events (0.6%) were registered for incident COVID-19 (including 4 hospital admissions) and 1030 (2.7%) events for all-cause mortality. No COVID-19 related deaths were registered. Study participants with incident COVID-19 were younger, less frequently established CVD, and lower concentrations of cTnI.

Most of these differences were attenuated after adjustment for age and sex (Table 1). After adjustment for age and sex, the difference in cTnI between groups was 8.2% (95% CI, −2.9 to 19.4%). Lower concentrations of log-transformed cTnI were associated with incident COVID-19 (subdistribution hazard ratio [sHR] 0.77; 95% CI, 0.67–0.89). This association was no longer significant in adjusted analysis (adjusted sHR [asHR] 1.02; 95% CI, 0.87–1.20). The results were similar when limiting analysis to 2020, before the initiation of the Norwegian coronavirus immunization program (asHR 0.90; 95% CI, 0.66–1.22). There was no difference in the associations of cTnI with incident COVID-19 in study participants with (asHR 1.27; 95% CI, 0.72–2.25) or without established CVD (asHR 1.01; 95% CI, 0.86–1.19, P for interaction = 0.72). cTnI above the sex-specific 99th percentile (asHR 0.73, 95% CI, 0.18–2.95) or established CVD per se (asHR 0.77; 95% CI, 0.41–1.42) were not associated with incident COVID-19. cTnI did not improve the c statistics or NRI when added to a basic risk model constructed on age, sex, and established risk factors for severe COVID-19 (c index 0.686; 95% CI, 0.654–0.718, vs 0.686; 95% CI, 0.654–0.718, P for comparison = 0.97; NRI 0.087, 95% CI, −0.204 to 0.240). C-reactive protein (CRP) was not associated with incident COVID-19 (c index 0.514; 95% CI, 0.474–0.554), and there were no model improvements when cTnI was added to the basic risk model and CRP.

In conclusion, our study did not permit investigations of COVID-19 severity, as we acquired data on incident COVID-19 from the national registry of communicable diseases. The number of COVID-19 events was low, as Norway has been modestly affected by the ongoing pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing is performed on clinical indication and accordingly non-systematic, possibly underestimating the true number of COVID-19 patients. The number of hospital admissions was low, barring any meaningful analyses in this regard.

In conclusion, our study does not support the hypothesis of an association between subclinical myocardial injury and incident COVID-19. cTnI did not improve the c statistics or NRI when added to a basic risk model constructed on age, sex, and established risk factors for severe COVID-19 (c index 0.686; 95% CI, 0.654–0.718, vs 0.686; 95% CI, 0.654–0.718, P for comparison = 0.97; NRI 0.087, 95% CI, −0.204 to 0.240). C-reactive protein (CRP) was not associated with incident COVID-19 (c index 0.514; 95% CI, 0.474–0.554), and there were no model improvements when cTnI was added to the basic risk model and CRP.

In this population-based study with prospective measurement of cTnI, we found no association between subclinical myocardial injury, established CVD, and risk of incident COVID-19. Considering the established link between CVD, cardiac troponins, and COVID-19 severity (1), it is surprising that study participants with incident COVID-19 exhibited lower concentrations of cTnI. These study participants, however, were considerably younger, consistent with the demographic COVID-19 trends in Europe (5), and the absolute differences and prognostic properties of cTnI were attenuated in adjusted analyses.

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Table 1. Baseline characteristics according to incident COVID-19.²

|                          | Total cohort (n = 37,835) | No COVID-19 (n = 37,598) | Incident COVID-19 (n = 237) | Unadjusted | Adjusted for age and sex |
|--------------------------|---------------------------|---------------------------|-----------------------------|------------|--------------------------|
|                          | n                         | Value                     | n                           | Value      | P                        |
| Male sex, n (%)          | 37,835                    | 17,081 (45.1%)            | 37,598                      | 17,074 (45.1%) | >0.99 | 0.85 |
| Age, years               | 37,835                    | 55.4 (41.1–68.4)          | 37,598                      | 55.5 (41.2–68.5) | <0.001 | <0.001 |
| Current smoking, n (%)   | 37,060                    | 3228 (8.7%)               | 36,837                      | 3219 (8.7%) | 0.012 | 0.034 |
| Higher education, n (%)  | 37,001                    | 13,817 (37.3%)            | 36,781                      | 13,732 (37.3%) | 0.73 | 0.27 |
| Medical history          |                           |                           |                             |            |                           |
| Diabetes mellitus, n (%) | 36,816                    | 2257 (6.1%)               | 36,594                      | 2247 (6.1%) | 0.40 | 0.58 |
| Angina pectoris, n (%)   | 35,543                    | 1117 (3.1%)               | 35,331                      | 1112 (3.1%) | 0.69 | 0.32 |
| Myocardial infarction, n (%) | 35,733                  | 1422 (4.0%)               | 35,520                      | 1418 (4.0%) | 0.16 | 0.86 |
| Heart failure, n (%)     | 35,486                    | 654 (1.8%)                | 35,273                      | 651 (1.8%) | >0.99 | 0.22 |
| Atrial fibrillation, n (%) | 35,286                  | 1884 (5.3%)               | 35,078                      | 1879 (5.4%) | 0.06 | 0.66 |
| Stroke, n (%)            | 35,532                    | 1170 (3.3%)               | 35,319                      | 1166 (3.3%) | 0.33 | 0.76 |
| Any cardiovascular disease, n (%) | 37,835               | 4736 (12.5%)             | 37,598                      | 4724 (12.6%) | <0.001 | 0.36 |
| Cancer, n (%)            | 35,795                    | 2852 (8.0%)               | 35,585                      | 2842 (8.0%) | 0.10 | 0.77 |
| Antihypertensive therapy, n (%) | 37,835              | 8739 (23.1%)            | 37,598                      | 8715 (23.2%) | <0.001 | 0.26 |
| Lipid lowering therapy, n (%) | 37,835            | 5994 (15.8%)             | 37,598                      | 5979 (15.9%) | <0.001 | 0.30 |
| Body mass index, kg/m²   | 37,420                    | 26.8 (24.0–30.0)          | 37,184                      | 26.8 (24.0–30.0) | 0.16 | 0.06 |
| Waist-to-hip ratio       | 37,838                    | 0.95 (0.90–1.01)          | 37,598                      | 0.95 (0.90–1.01) | 0.52 | 0.008 |
| Heart rate, bpm           | 36,319                    | 71 (64–80)                | 36,088                      | 71 (64–80) | 0.21 | 0.37 |
| Systolic blood pressure, mmHg | 37,675               | 126 (115–139)            | 37,439                      | 126 (115–139) | <0.001 | 0.28 |
| Diastolic blood pressure, mmHg | 37,675             | 72 (65–79)                | 37,439                      | 72 (65–79) | <0.001 | 0.041 |
| Total cholesterol, mg/dL  | 37,835                    | 5.2 (4.4–6.0)             | 37,598                      | 5.2 (4.4–6.0) | 0.008 | 0.31 |
| HDL cholesterol, mg/dL   | 37,835                    | 1.3 (1.1–1.6)             | 37,598                      | 1.3 (1.1–1.6) | 0.004 | 0.005 |
| Hb A₁c, %                 | 37,694                    | 5.2 (5.0–5.5)             | 37,459                      | 5.2 (5.0–5.5) | <0.001 | 0.64 |
| Hemoglobin, g/dL          | 37,699                    | 14.6 (13.7–15.5)          | 37,464                      | 14.6 (13.7–15.5) | 0.80 | 0.09 |
| White blood cell count, 10⁹/L | 37,697                | 6.7 (5.7–7.9)             | 37,462                      | 6.7 (5.7–7.9) | 0.07 | 0.16 |
| eGFR, ml/min/1.73m²      | 37,835                    | 90.0 (80.0–105.0)         | 37,598                      | 90.3 (80.0–105.0) | <0.001 | 0.48 |
| CRP, mg/L                | 37,835                    | 1.3 (0.6–2.7)             | 37,598                      | 1.3 (0.6–2.7) | 0.45 | 0.007 |
| Cardiac troponin I, ng/L  | 37,835                    | 1.8 (0.6–3.5)             | 37,598                      | 1.8 (0.6–3.5) | <0.001 | 0.15 |

²Data are reported as absolute numbers (proportion) or median (interquartile range) unless otherwise stated.

Any cardiovascular disease = history of angina pectoris, myocardial infarction, heart failure, atrial fibrillation, and/or stroke.

Abbreviations: bpm, beats per minute; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; NA, not applicable.

To convert cholesterol concentrations from mg/dL to mmol/L, multiply by 0.02586.

Detectable cardiac troponin I = above or at limit of detection (1.2 ng/L). Cardiac troponin I concentrations below the limit of detection were assigned a value of 0.6 ng/L.
COVID-19 in predominantly healthy community dwellers. Populations with higher incidence of severe COVID-19 are needed to assess whether cTnI is an independent risk factor for hospital admission in COVID-19.

Nonstandard Abbreviations: CVD, cardiovascular disease; HUNT Study, Trøndelag Health Study; cTnI, cardiac troponin I; asHR, adjusted subdistribution hazard ratio.

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