Vascular risk factors, Framingham risk score, and COVID-19: community-based cohort study

G. David Batty *1 and Mark Hamer 2

1Department of Epidemiology & Public Health, University College London, UK; and 2Division of Surgery & Interventional Science, University College London, UK

Introduction

Evidence from prognostic studies of groups of COVID-19 patients suggest that those admitted to hospital with existing cardiovascular disease (CVD) experience worse outcomes relative to those who are CVD-free, as evidenced by their markedly increased risk of progression to intensive care and death. 1 While obesity also appears to be related to unfavourable outcomes in COVID-19 patients, 2 it is unknown whether this and other established CVD risk factors, as distinct from CVD itself, are associated with the occurrence of the infection, particularly in community samples. More generally, there is evidence from cardiovascular research to suggest that prognostic characteristics may reveal opposing relationships to those apparent for aetiological factors. For instance, British people of South Asian descent have a higher incidence of coronary disease but lower mortality once diagnosed with the condition. 3 For the first time to our knowledge, we therefore examined whether unfavourable levels of classic CVD risk factors, both individually and collectively within the Framingham model, 4 were implicated in the primary prevention of COVID-19 in a community-based prospective cohort study. Assessing the predictive value of the Framingham index for COVID-19 has potential clinical utility as this tool is widely used in general practice in many countries.

Methods

We used data from UK Biobank, a prospective cohort study, the sampling and procedures of which have been well described. Baseline data collection took place between 2006 and 2010 across centres in the UK, giving rise to a sample of 502 655 people (448 919 from England) aged 40–69 years (response rate 5.5%). 5 Ethical approval was received from the North-West Multi-centre Research Ethics Committee.

Cigarette smoking, physician-diagnosed diabetes, highest educational attainment, ethnicity, and physical activity in the previous month were self-reported using standard enquiries. Body mass index was based on direct measurements of height and weight. Blood pressure was measured in the seated position with the average of two readings used, and total cholesterol and HDL cholesterol were assayed from a non-fasting blood sample. The Framingham risk score was computed using sex-specific multivariable functions comprising age, total and HDL cholesterol, systolic blood pressure, smoking, and diabetes status. 5 Provided by the Public Health England agency, data on COVID-19 covered the period 16 March until 26 April 2020. Nose and/or throat swabs were taken from hospitalized patients, and detection of SARS-CoV-2 can be regarded as an indication of a severe manifestation of the disease.

Discussion

Evidence from prognostic studies of hospitalized COVID-19 patients suggests that a series of physical characteristics are linked to progression to intensive care and death, 1,2 and these relationships were also apparent in the present analyses for age, being male, existing diabetes, and overweight/obesity in relation to hospitalization for the infection (Table 1). Further, a history of CVD was related to an almost doubling of risk of subsequent COVID-19 (1.82; 1.60–2.08). The replication of these relationships in the present data set gives us confidence in our novel results for CVD risk indices. People in the intermediate risk groups of the Framingham algorithm experienced a lower risk of COVID-19. A similar pattern of association was apparent for COVID-19 and age which itself is the strongest predictor of CVD of those that comprise this index. It maybe therefore that this “J”-shaped relation between the Framingham score and COVID-19 is largely generated by the impact of age.
Follow-up for COVID-19 events was up to 14 years after baseline examination, and this can raise concerns about the stability of baseline data. After a median of 4.4 years, a representative subgroup of study participants were reassessed (n = 19 772). For those risk factors featured in the Framingham algorithm that were captured at retesting, test–re-test correlation coefficients were high for body mass index (0.93), systolic blood pressure (0.65), and cigarette smoking (0.84). This suggests that risk factors gathered at baseline have a high degree of stability. It is also the case that the UK Biobank study sample is based on the recruitment of 5.5% of the target population. As has been demonstrated, the data are therefore inappropriate for estimation of risk factor prevalence or disease occurrence. These observations do not, however, seem to influence reproducibility of the association of established risk factors for non-communicable disease such as vascular disease, and we think that the same reasoning can be applied to relationships with communicable diseases.

In conclusion, in the present study, established CVD risk factors revealed associations with hospitalization for COVID-19 at a magnitude similar to those apparent for vascular outcomes. For people in the highest risk groups, the Framingham Risk Score also offered some predictive utility and, if replicated, this finding may have implications for clinical practice and the identification of at-risk groups to be targeted when an effective vaccine is developed.

### Data availability

Data from the UK Biobank (https://www.ukbiobank.ac.uk/) are available to bona fide researchers on application.

### Authors’ contributions

G.D.B. and M.H. both generated the idea for the present analyses; G.D.B. prepared a draft of the manuscript; M.H. analysed the data and edited the draft manuscript. Part of this research has been conducted using the UK Biobank Resource under Application 10279.

### Conflict of interest

None declared.

### Funding

G.D.B. is supported by the Medical Research Council (MR/P023444/1) and the US National Institute on Aging (1R56AG052519-01; 1R01AG052519-01A1); M.H. is supported through a joint award from the Economic Social Research Council and Medical Research Council (RES-579-47-0001).

### References

1. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging 2020;12:6049–6057.
2. Simonnet A, Chetboun M, Poissy J, Raverdy V, Niolette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020;doi: 10.1002/oby.22831
3. Zaman MJ, Philipson P, Chen R, Farag A, Shipley M, Marmot MG, Timmis AD, Hemingway H. South Asians and coronary disease: is there discordance between effects on incidence and prognosis? Heart 2013;99:729–736.
4. D’Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–753.
5. Sudow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peckman T, Collins R. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
6. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ 2020;368:m131.

### Table 1

| Individual risk factors | COVID-19 cases/number at risk | Age- and sex-adjusted RR (95% CI) | Adjusted<sup>a</sup> RR (95% CI) |
|-------------------------|-------------------------------|-----------------------------------|----------------------------------|
| Age (per 5 year increase) | 700/356 914                  | 1.07 (1.02–1.12)                  | 1.05 (1.00–1.11)                 |
| Male                    | 400/162 747                   | 1.59 (1.37–1.84)                  | 1.69 (1.45–1.98)                 |
| Current smoking         | 91/35 252                     | 1.57 (1.24–1.99)                  | 1.46 (1.15–1.86)                 |
| Physical inactivity     | 86/21 332                     | 2.31 (1.84–2.84)                  | 1.58 (1.25–2.00)                 |
| Obesity/overweight      | 544/237 440                   | 1.63 (1.36–1.95)                  | 1.45 (1.21–1.74)                 |
| Diabetes                | 63/17 266                     | 1.77 (1.36–2.29)                  | 1.31 (1.01–1.74)                 |
| Systolic blood pressure (per SD increase) | 700/356 914                  | 1.03 (0.96–1.12)                  | 0.99 (0.92–1.08)                 |
| Total cholesterol (per SD increase) | 700/356 914                  | 0.82 (0.76–0.89)                  | 0.86 (0.80–0.93)                 |
| HDL (per SD increase)   | 700/356 914                   | 0.70 (0.64–0.77)                  | 0.77 (0.70–0.85)                 |
| Framingham risk score (quintiles) | 700/356 914                  |                                  |                                  |
| ≤9                      | 162/91 892                    | 1.0 (ref)                         | 1.0 (ref)                        |
| 10–12                   | 116/84 208                    | 0.78 (0.62–1.0)                   | 0.71 (0.56–0.90)                 |
| 13–14                   | 125/68 984                    | 1.03 (0.82–1.30)                  | 0.91 (0.72–1.15)                 |
| 15–16                   | 147/62 248                    | 1.34 (1.07–1.68)                  | 1.15 (0.91–1.45)                 |
| ≥17 (highest risk)      | 150/49 582                    | 1.72 (1.38–2.15)                  | 1.35 (1.05–1.70)                 |

<sup>a</sup>Sample sizes correspond to full analytical sample for analyses of continuous risk factors, and the category of interest in analyses of categorical risk factors.

<sup>b</sup>Adjusted for age, sex, body mass index, physical activity, alcohol, education, and ethnicity.

<sup>c</sup>Adjusted for body mass index, physical activity, alcohol, education, ethnicity.

CI, confidence interval; RR, relative risk. SD, standard deviation.