Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS) are frequent post–acute COVID-19 sequelae (PACS) 

**Background:** Postural orthostatic tachycardia syndrome (POTS) and myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) are debilitating diseases leading to heart racing, fainting, and extreme fatigue and malaise, respectively.

**Results:** Among 2'521'812 COVID-19 compared to 4'233'145 test negative patients, overall IRRs were 1.24, 1.22, and 1.12 for POTS symptoms, ME/CFS symptoms and diagnoses, respectively (Fig. 1). Increased rates mainly occurred among children and elderly. Autoimmune diseases and diabetes mellitus (DM, control) did not yield increased rates.

Among all 34'549'575 individuals in general database populations, IRRs of POTS and ME/CFS diagnoses ranged 17-1'477/100'000 person-years (py) and 2-473/100'000 py, respectively (Fig. 2, depending on the database). IRR of MIS ranged lowest with 0.4-16/100’000 py and those of DM as a benchmark ranged 8-86/100’000 py. IRRs largely depended on the care setting.

**Methods:** Descriptive cohort study in electronic health records and claims from various health care settings in the UK, Netherlands, Norway, Spain, France, Estonia, Korea, and USA (September 2020 until latest available data). Patients had at least 365 days of prior observation (general population), a SARS–Cov–2 negative test (comparator) or a COVID–19 record (exposed patients). We assessed postural orthostatic tachycardia syndrome (POTS), myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS), multi-inflammatory syndrome (MIS), and several autoimmune diseases. For contextualisation, we assessed any diabetes mellitus (DM).

Meta-analysed crude incidence rate ratios (IRR) of outcomes measures after COVID-19 versus negative testing yield the ratios of absolute risks. Incidence rates (IR) of the outcomes in the general population describe the total disease burden.

**Limitation:** We neither matched groups nor adjusted for confounders, yet we observed sex and age (important confounders) to be mostly balanced. Secondary care data are not representative of the general population.