Appendix S1

SUPPLEMENTARY MATERIAL

Methods

Collection of Lifestyle and Demographic Factors

At the start of the Rotterdam Study, participants provided information on their sex and date of birth. Age was calculated at the time of chronic pruritus (CP) questionnaire completion. Body mass index (BMI) was derived from height and weight measurements obtained during research centre visits.

Additional lifestyle and demographic factors were collected through structured home interviews. Smoking status was categorized as never, former, or current smoker of cigarettes. Alcohol consumption was classified into four groups: non-drinker, light drinking (≤1 occasion/month, any quantity), moderate drinking (multiple occasions/month with ≤9 drinks per occasion), and heavy drinking (multiple occasions/week with ≥10 drinks regularly). Educational level was categorized as low (primary education), medium (lower to intermediate vocational education), or high (general secondary education or higher). Skin colour was categorized as pale-to-white, white-to-olive, or dark during a dermatological assessment, performed by dermatology-trained physicians (1).

Assessment of Dermatological Factors

Dermatological conditions were assessed through both self-report and skin examinations by dermatology-trained physicians. During home interviews conducted by research assistants, participants reported any history of dermatological conditions. Possible atopic dermatitis (AD) was defined according to the UK Working Party Criteria, which require a self-reported history of an itchy skin condition with involvement of typical areas such as skin creases (2). Psoriasis was defined as a self-reported physician diagnosis. Presence of dry skin over the past year was recorded.

Dermatological assessments were performed by dermatology-trained physicians during full-body skin examinations (FBSE) at the research centre. AD was identified by the presence of erythematous, scaly, lichenified, and excoriated patches in common flexural areas. Psoriasis was assessed as sharply demarcated erythematous, scaly, thickened plaques. Dry skin was categorized as either localized (on the extensor surfaces of the extremities) or generalized.

Assessment of Systemic and Neurological conditions, and Medication Use

Systemic and neurological conditions were assessed through a combination of self-report, measurements, and medical record review. Self-reported history of asthma was obtained from the same questionnaire as the CP questions. History of thyroid disease, including hyperthyroidism and hypothyroidism, was assessed via self-report during interviews. Renal function was measured with the estimated glomerular filtration rate (eGFR).

Liver stiffness (fibrosis) was evaluated using transient elastography (FibroScan; Echosens, Paris, France) by a hepatology-trained physician. Steatotic liver disease included both MASLD (metabolic dysfunction-associated steatotic liver diseases) and MetALD (MASLD with alcohol intake exceeding 140 gram/week for women and 210 gram/week for men). Diabetes mellitus was considered present if participants met any of the following criteria: fasting plasma glucose level of 7.0 mmol/L or higher, non-fasting glucose level of 11.1 mmol/L or higher, or use of antidiabetic medicine. Information on previous stroke events was obtained from hospital records. Polyneuropathy screening consisted of multiple components: a symptom questionnaire, neurological examination of the legs, nerve conduction studies of the sural nerves, and medical record review. Based on these data, participants were categorized as having no, possible-to-probable, or definite chronic axonal polyneuropathy. Medication use was self-reported during home interviews and categorized according to the Anatomical Therapeutic Chemical (ATC) classification. Medication groups included: cardiovascular medications (e.g., anti-hypertensives, diuretics, vasoprotectives (including antivaricose and capillary stabilizing agents), beta-blockers, calcium-blockers, and ACE-inhibitors) and central nervous system medications (e.g., anesthetics, analgesics, anti-epileptics, psycholeptics, psychoanaleptics, and others). These medication groups were selected based on existing literature (3) and their availability in the Rotterdam Study.

Assessment of Psychological symptoms, Sleep, and Quality of Life

Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression scale (CES-D) scores, with a score of 16 or higher indicating clinically relevant depressive symptoms (4, 5). Anxiety symptoms were measured using a harmonized 6-item version of the Hospital Anxiety and Depression Scale - Anxiety subscale (HADS-A), described in the next section (6). Both CES-D and HADS-A scores were collected during home interviews.

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a validated 19-item questionnaire covering seven domains of sleep (7). The global PSQI score ranges from 0 to 21, with higher scores reflecting poorer sleep quality. A global score >5 was used to define poor sleep quality.

HADS-A 6-item version

In the Rotterdam Study, the items used to assess anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS) varied slightly across examination rounds. As a result, the standard HADS anxiety subscale and its validated cut-off could not be consistently applied across all cohorts. To allow for pooled analyses, a harmonized 6-item version (called HADS-A-6 in the remainder of the article) was created based on the overlapping items available in each round. While this version allows for cross-cohort comparability, it lacks a validated clinical cut-off and should be interpreted with caution.

The six included items were:

1. I have felt tense or ‘wound up’ lately.
2. I get a frightening feeling like something awful is about to happen.
3. I have been feeling worried lately.
4. I get a sort of frightened feeling like ‘butterflies’ in the stomach.
5. I have been feeling restless lately.
6. I get sudden feelings of panic or fear.

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