1.99, 95% CI: 1.13-3.50). The weighted RD of gynecological cancers was 42.58 (95% CI: 11.77-69.32) per 100,000 person-years, with the rate notably elevated among patients aged over 51 years (IRR=2.09, 95% CI: 1.02-4.26), and those diagnosed with psychotic disorders (IRR=9.69, 95% CI: 1.32-71.10).

In head-to-head drug comparisons, the increased rate remained statistically significant for the quetiapine-haloperidol and quetiapine-risperidone comparisons (IRR=2.27, 95% CI: 1.21-4.26; and IRR=2.20, 95% CI: 1.10-4.37). Regarding gynecological cancer subcategories, elevated risks of endometrial cancer (IRR=1.94, 95% CI: 1.02-3.69) and ovarian cancer (IRR=3.68, 95% CI: 1.17-11.56) were observed. The increased risk of cervical or vaginal cancer did not reach statistical significance (IRR=1.33, 95% CI: 0.44-4.04 and IRR= 2.14, 95% CI: 0.43-10.73, respectively). Similar results were seen in the sensitivity analyses, including the positive control outcome analysis on breast cancer (IRR=1.63, 95% CI: 1.10-2.43), with the negative control outcome analysis showing a non-significant IRR close to 1 (IRR=0.96, 95% CI: 0.37-2.55).

To the best of our knowledge, this is the first cohort study, and the largest real-world study, to compare prolactin-increasing with prolactin-sparing antipsychotic use in terms of incidence of gynecological cancers. Findings suggest a two-fold increased rate of this incidence among users of prolactin-increasing antipsychotics compared with those using prolactin-sparing antipsychotics, particularly evident for ovarian and endometrial cancers, but with small RDs, i.e., approximately one case per 2,300 person-years. Preclinical studies suggesting biological links[8] and observational studies supporting an empirical association[9] are far from scarce, with preliminary evidence suggesting that prolactin may promote the growth of ovarian and endometrial surface epithelial cells, enhance ovarian cancer cell survival and migration, and inhibit apoptosis[8]. Key limitations of the study include the lack of randomization and potentially limited generalizability beyond Chinese populations.

In conclusion, our study showed that prolactin-increasing antipsychotics are associated with an increased rate of gynecological cancers compared with prolactin-sparing antipsychotics, although the RD is small, entailing little clinical significance.

Francisco Tsz Tsun Lai[1-4], Wenxin Tian[1], Yuqi Hu[1], Cuiling Wei[1], Qi Sun[1], Song Song[1,2], Lingyue Zhou[1], Yue Wei[1,2], Shan Luo[3,5], Amy Pui Pui Ng[3], Joe Kwun Nam Chan[6], Heidi Ka Ying Lo[6], Esther Wai Yin Chan[1,2], Stanley Sau Ching Wong[7], Wing Chung Chang[6,8]

[1]Department of Pharmacology and Pharmacy, Centre for Safe Medication Practice and Research, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; [2]Laboratory of Data Discovery for Health, Hong Kong Science Park, Sha Tin, Hong Kong; [3]Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; [4]Advanced Data Analytics for Medical Science, Hong Kong, Hong Kong; [5]School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; [6]Department of Psychiatry, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; [7]Department of Anaesthesiology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; [8]State Key Laboratory of Brain and Cognitive Sciences, University of Hong Kong, Hong Kong

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Predicting epigenetic aging by the transdiagnostic internalizing spectrum vs. depressive and anxiety syndromes

Depression and anxiety are linked with higher risk for multimorbidity[1] and all-cause mortality[2]. In health research, they are often indexed as binary syndromes or symptom counts, reflective of traditional diagnostic models. However, there has long been evidence supporting dimensional and hierarchical conceptualizations of psychopathology[3], wherein the widespread comorbidity among mood and anxiety disorders is modeled in terms of a broader, transdiagnostic internalizing spectrum[4].

Evidence has accumulated that the broader internalizing factor has superior reliability and predictive validity relative to traditional diagnoses, and that its components have shared genetic diatheses, environmental risk factors, childhood antecedents, and treatment responses[5]. Kim et al[6] found that the internalizing spectrum significantly predicted mortality risk over a 20-year period (hazard ratio, HR=1.12, p<0.01), while disorder-specific variability (i.e., residuals net of their common variance) did not have predictive power (HRs=0.94-1.02). These results suggest that psychopathology-related mortality risk is captured at the level of the broader spectrum.

Less is known about relations between psychopathology and the biological aging processes underlying morbidity and mortality. Epigenetic alteration is considered one of the "hallmarks of aging", as changes in gene expression can result in the development of many age-related pathologies[7]. One such epigenetic pro-

cess is DNA methylation, or the binding of methyl group molecules to genes in a manner that inhibits or promotes their transcription. Strong associations have been observed between age and methylation in some regions of the genome, leading to the development of epigenetic clocks designed to index biological age as distinct from chronological age. Individuals are said to experience epigenetic age acceleration when their biological (or epigenetic) age exceeds their chronological age. Epigenetic age acceleration as indexed by recent measures (e.g., GrimAge, DunedinPACE) has been validated in novel samples as a replicable predictor of aging-related morbidity and mortality[8].

Epigenetic aging also correlates with a variety of psychosocial and environmental variables, including depression[9]. However, to our knowledge, it has not been studied in relation to the broader internalizing spectrum in adulthood. Given the robust evidence on the structure of psychopathology, modeling a latent internalizing liability might increase predictive power for epigenetic aging and help explain inconsistencies in prior research, as it has with mortality[6]. Consistent with the notion that health-relevant variability within traditional disorders is captured by an overarching liability, we hypothesized that a transdiagnostic internalizing factor would predict future epigenetic age acceleration, and that the variance specific to symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD), and panic disorder (net of internalizing) would not.

DNA methylation profiling was conducted on 1,309 participants from the National Survey of Midlife Development in the United States (MIDUS). Sociodemographic, psychopathology, and other health factors were assessed during MIDUS survey visits (mean age 51.3; Time 1), and blood was collected for the later Biomarker project (mean age 54.0; Time 2). Whole blood samples were subject to DNA extraction and underwent genome-wide methylation profiling using Illumina EPIC microarrays. Methylation data were scored with existing algorithms to compute four measures of epigenetic age (the Hannum, Horvath, PhenoAge, and GrimAge2 clocks) and the DunedinPACE measure of epigenetic age acceleration.

Exploratory structural equation modeling was then used to examine the covariation among DunedinPACE and the residuals of the four clocks after they were regressed on chronological age. A two-factor model fit the data well. The first factor reflected the earlier Hannum and Horvath measures designed to predict cross-sectional state (age, health state) and the second reflected the later ones developed to predict change in health (GrimAge2 and DunedinPACE). Thomson's factor scores were carried forward and labeled "state-predictive" and "decline-predictive" epigenetic aging. Confirmatory factor analysis was used to model a transdiagnostic internalizing factor with three indicators: continuous symptom counts for MDD, GAD and panic disorder as assessed by the Composite International Diagnostic Interview - Short Form. All three indicators had meaningful and statistically significant factor loadings (λ>0.40, p<0.001).

Structural equation models were then fit that tested the prediction of epigenetic aging (both state and decline factors) by the internalizing factor (Model 1), each of the symptom count variables (Models 2-4), and the residuals for each of the symptom count variables net of the internalizing factor (Models 5-7). In all models, the focal psychopathology variable (Time 1 internalizing or a symptom count) predicted later (Time 2) epigenetic aging. The focal psychopathology variable was regressed on the following six covariates: age, sex, education level, race, body mass index, and smoke pack years. Then the epigenetic aging variable was regressed on the psychopathology variable and the same covariates. All models were fit in Mplus using maximum likelihood estimation with cluster robust (Huber-White) standard errors to account for the nested, within-family structure of the data from siblings in the MIDUS study.

The latent internalizing factor was significantly associated with decline-predictive epigenetic age acceleration (Model 1: β=0.11, p=0.001). Decline-predictive epigenetic age acceleration was also significantly associated with symptoms of MDD (Model 2: β=0.07, p=0.001), but not those of GAD (Model 3: β=0.05, p=0.017) or panic disorder (Model 4: β=0.03, p=0.216). None of the symptom count residuals (net of internalizing) were significantly associated with decline-predictive epigenetic aging (Models 5-7: β=–0.03 to 0.02, p values >0.350). Across models, none of the psychopathology variables were significantly associated with state-predictive epigenetic aging (β=–0.01 to 0.04, p values >0.250). Models accounted for 32-35% of variance in decline-predictive epigenetic aging and 3-4% in state-predictive epigenetic aging (inclusive of covariates) (see also supplementary information).

These analyses evaluated the utility of the internalizing spectrum and symptoms of specific depressive and anxiety syndromes in predicting later epigenetic aging. Accelerated epigenetic aging in decline-predictive measures was significantly associated with greater internalizing and more depressive symptoms. GAD and panic disorder symptoms were nominally positive, but not significant predictors of epigenetic aging. As with mortality[6], the symptom-specific variability, net of internalizing, was not significantly associated with epigenetic aging. These findings suggest that differential methylation of CpG sites (i.e., regions in the DNA sequence where cytosine is followed by guanine in a specific direction) associated with blood biomarkers of morbidity and mortality (e.g., GrimAge) is linked with internalizing and related variables, suggesting a possible mechanism by which psychosocial experiences become biologically embedded.

Since analyses were observational (with a single time-sequenced measurement of focal constructs), little can be concluded about directionality or the role of unmeasured confounders. Additionally, methylation was measured from circulating blood samples, and it is unclear how effects may vary across tissues. Nonetheless, these results suggest that the variability within traditional depressive and anxiety disorders relevant to aging-related health is captured by the overarching internalizing spectrum. Each of the symptom counts had less predictive power than the internalizing spectrum and, critically, little to no predictive power net of internalizing.

Many possible mechanisms may underlie associations between psychopathology and biological aging (e.g., behavioral and genetic factors). However, the relationship may be directly causal, wherein

difficulties with internalizing signal inflammatory and immune-related pathways, potentially involving or leading to epigenetic alteration.

Colin D. Freilich[1], Frank D. Mann[2], Kristian E. Markon[1], Steve W. Cole[3], Robert F. Krueger[1]
[1]Department of Psychology, University of Minnesota, Minneapolis, MN, USA; [2]Department of Medicine, Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, USA; [3]Department of Psychiatry & Biobehavioral Sciences and Medicine, University of California, Los Angeles, CA, USA

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Promoting collaboration, harmonization and dissemination in depression research: the ECNP Depression Meta-Network

The European College of Neuropsychopharmacology (ECNP) is a pan-European scientific association in the fields of translational neuroscience and applied brain research. Its core mission is to help ensure that advances in the understanding of brain function and human behavior are translated into better treatments and enhanced public health.

To this purpose, the College makes use of a variety of tools. The best known is its annual congress, attracting over 6,000 participants every year. However, equally vital to ECNP's mission are its networks, established roughly 20 years ago. The ECNP networks are multi-disciplinary collaborative platforms that bring together researchers from across Europe to share ideas, discoveries and best practices in translational neuroscience. Designed to facilitate the collection of essential biological, clinical and therapeutic data in a robust and replicable way, the current 25 existing ECNP networks cover a range of disease-oriented as well as transnosological (e.g., digital health, experimental medicine, nutrition, suicide, resilience) research focus areas.

Until recently, there has been a notable omission from the list of ECNP networks: depression was not included. The reasons are manifold and partially hard to unearth from history. In the beginning, it might have been a simple miss, as the formation of new networks did not follow a structured process. Later on, there was the feeling that a network on depression might be so broad to make almost impossible to select its members, given the enormous breadth of the field, with many ECNP members working on depression from different perspectives.

On the other hand, it was increasingly clear that a network on depression was mandatory, and its lack became noticeable. Depressive disorder is the mental health condition with the largest impact on disease burden, about 6% of the worldwide population being affected in the past year[1]. Its economic and societal impact is huge, not only due to its direct health care costs, but especially to its indirect costs through work absenteeism and impact on caregivers. Unfortunately, existing first-line medication and psychotherapy treatments do not work for all persons, and both treatment gap and treatment inertia for depression are large, leaving many patients inadequately treated, resulting in a sizeable proportion of them suffering from what is called treatment-resistant depression[2,3]. Consequently, within ECNP there is already a strong focus on developing and implementing more appropriate detection, prevention and treatment strategies for depression.

Depression is also a large focus of attention for other ECNP stakeholders, such as patient and family organizations and regulators. Also within industry, there has been recent progress in the drug development field that is relevant for depression (e.g., treatments targeting the glutamate system[4], psychedelic medications). Novel neuromodulation strategies – such as transcranial magnetic stimulation, transcranial direct-current stimulation, and vagus nerve stimulation – are getting more and more attention. Adding to this, depression is a vastly heterogeneous condition, much more syndromal than any other mental disorder. Therefore, "depression" might even be considered a transdiagnostic construct.

To tackle these challenges, we built up the Depression Meta-Network[5], which explicitly connects the various already existing ECNP network activities, by selecting experts working on depression from every relevant network, to build a "network of networks". This Meta-Network was formed at the end of 2023.

The overarching goal of ECNP's Depression Meta-Network is to bring together leading (pre)clinical researchers, industry, regulators and patient representatives from Europe to accelerate, across various disciplines, the understanding of the aetiologies of the depressive syndrome and improve its primary prevention, screening, diagnosis, early intervention, treatment, and thereby outcomes.

Specific aims are the following: a) to serve as a "hub" for connecting different partners (clinicians, researchers, industry, regulators, other stakeholders) in the field of depression, to share expertise and results, discuss clinical/industry/research developments, obtain European grants, and advise on better conduct of clinical trials and selection of appropriate outcome measures; b) to collect