Elucidating the Comorbidity Trajectory subsequent to AD: The Cluster patterns and Genetic Contributions

Yi Xiao MD, MPH, Ph.D.

Department of Dermatology, Xiangya Hospital, Central South University

xiaoyixy@csu.edu.cn

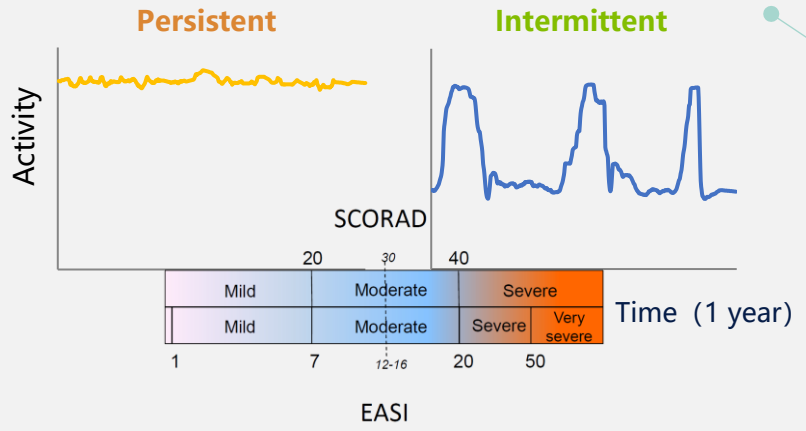
中南大學湘雅醫院
XIANGYA HOSPITAL CENTRAL SOUTH UNIVERSITY

Content

Study Background

The most recent Lancet review underscores the pronounced heterogeneity of atopic dermatitis.

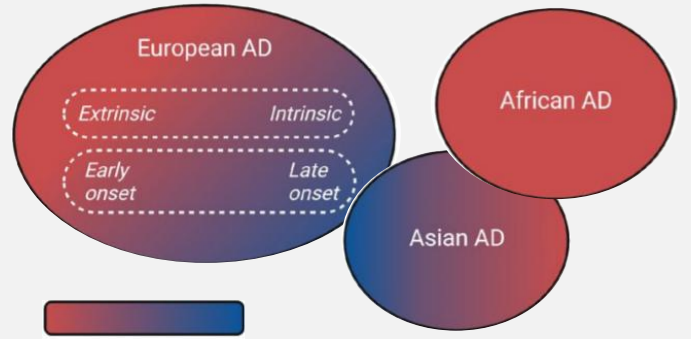
Disease Activity Patterns and Severity[1,4]



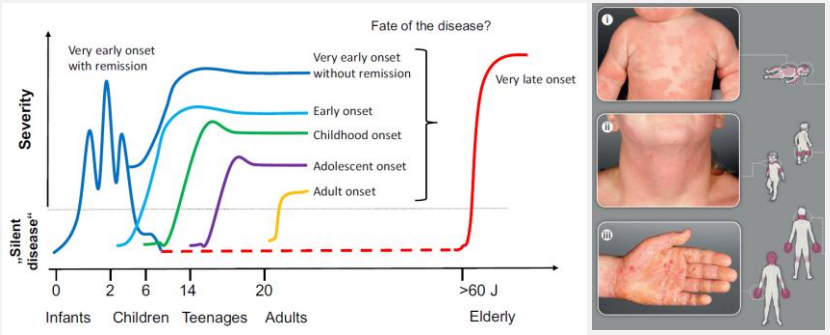
Th2-polarized inflammation is a hallmark of AD

T-helper (TH) cell expression levels vary across racial/ethnic groups[2]

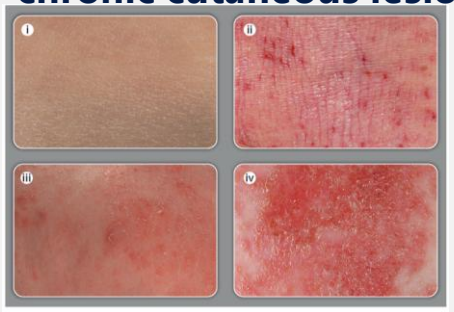
Intrinsic vs extrinsic (by IgE level)[2,3]



Age at Onset and Clinical Presentation[4,5]

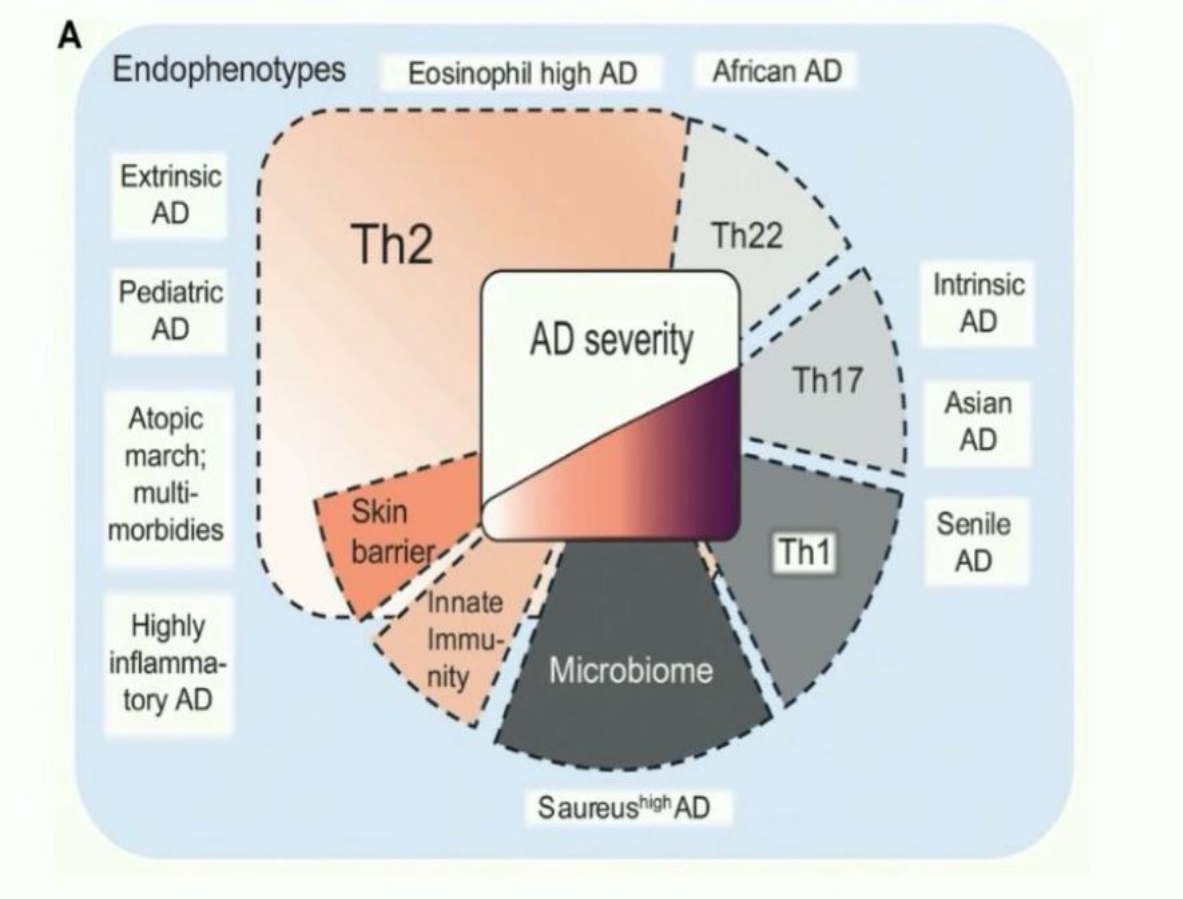


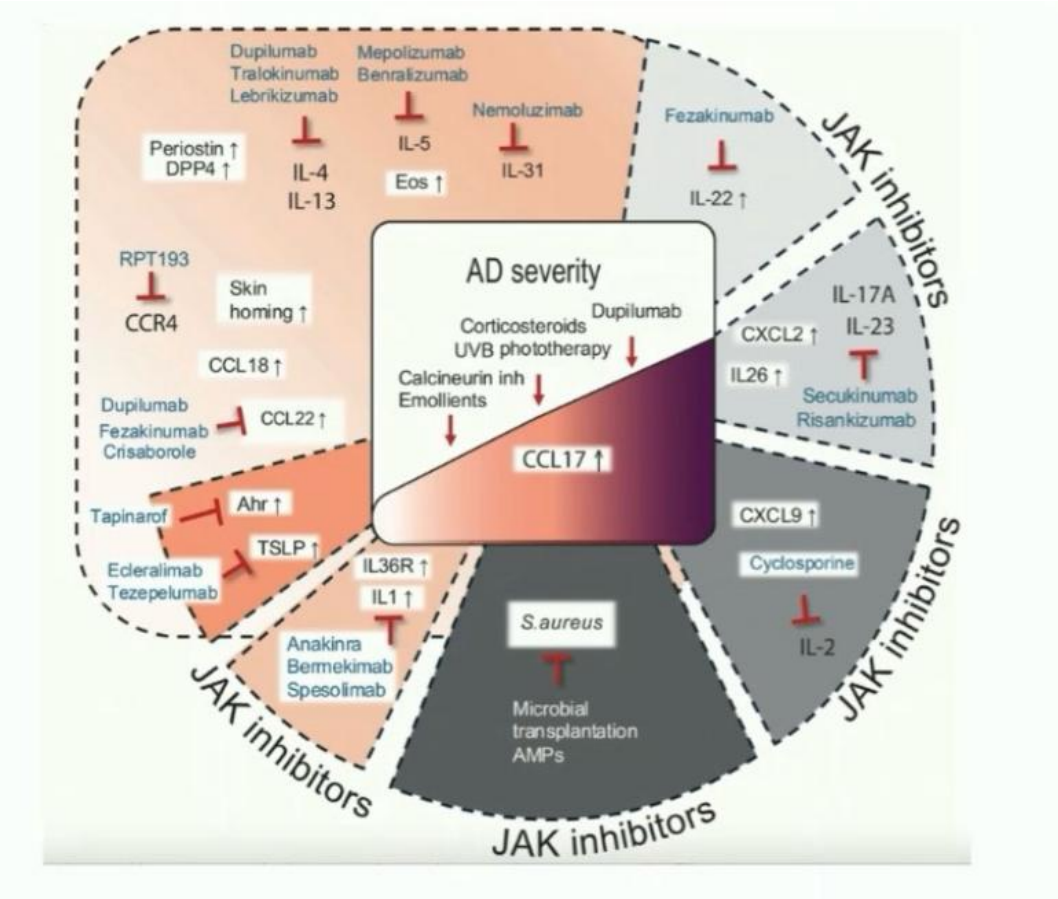
Acute, subacute, and chronic cutaneous lesions[5]



Guttman-Yassky E, et al. Lancet. 2025 Feb

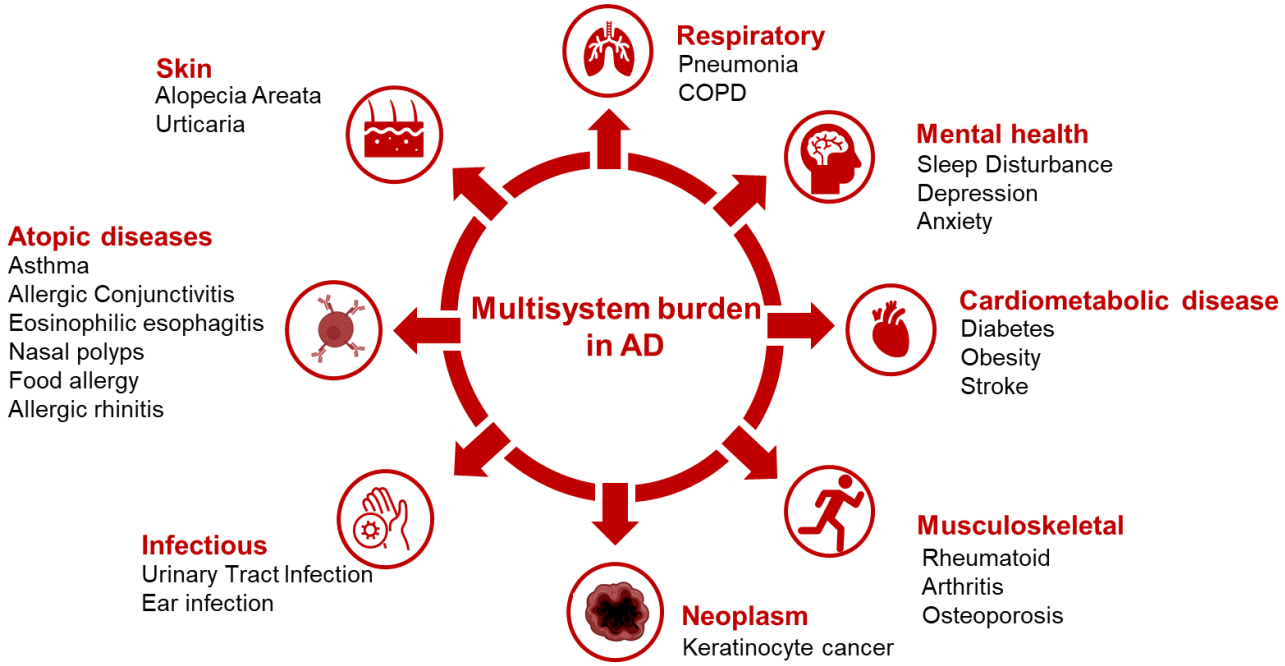
Study Background

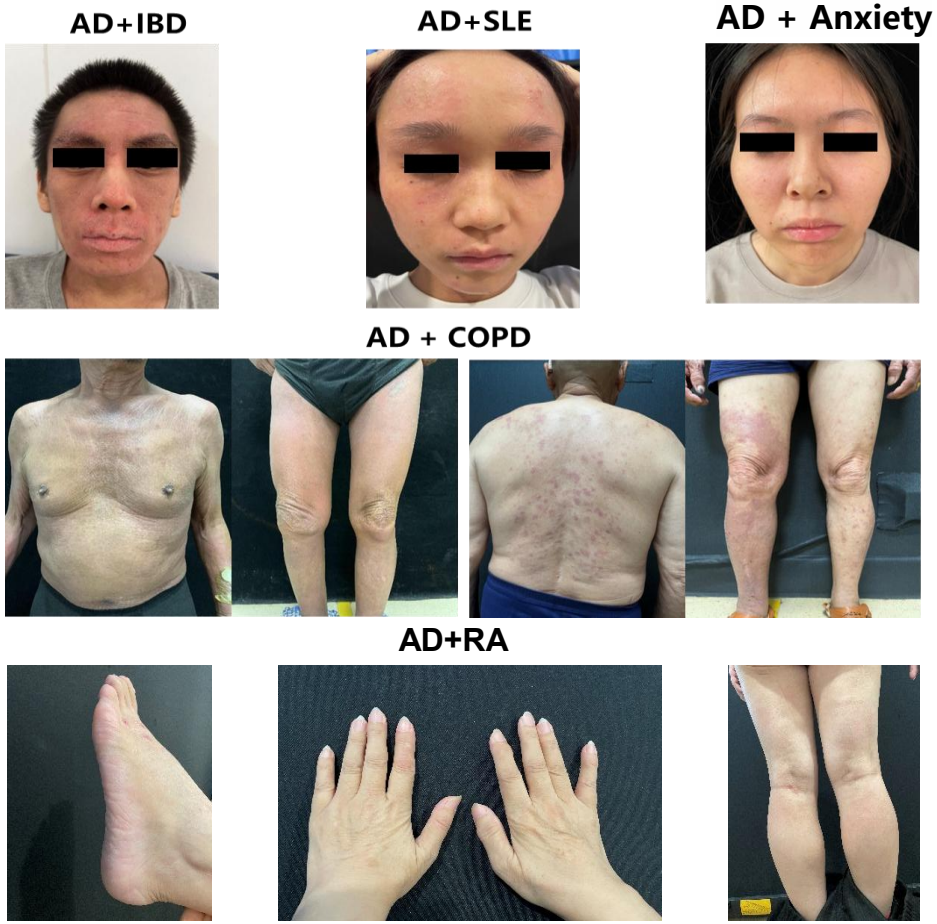




J Allergy Clin Immunol. 2025 Jul;156(1):24-40.e4.

Study Background: Co-occurrence comorbidities of AD.





Do the comorbidities in AD exhibit heterogeneity?

How the different comorbidities impact clinical treatment.

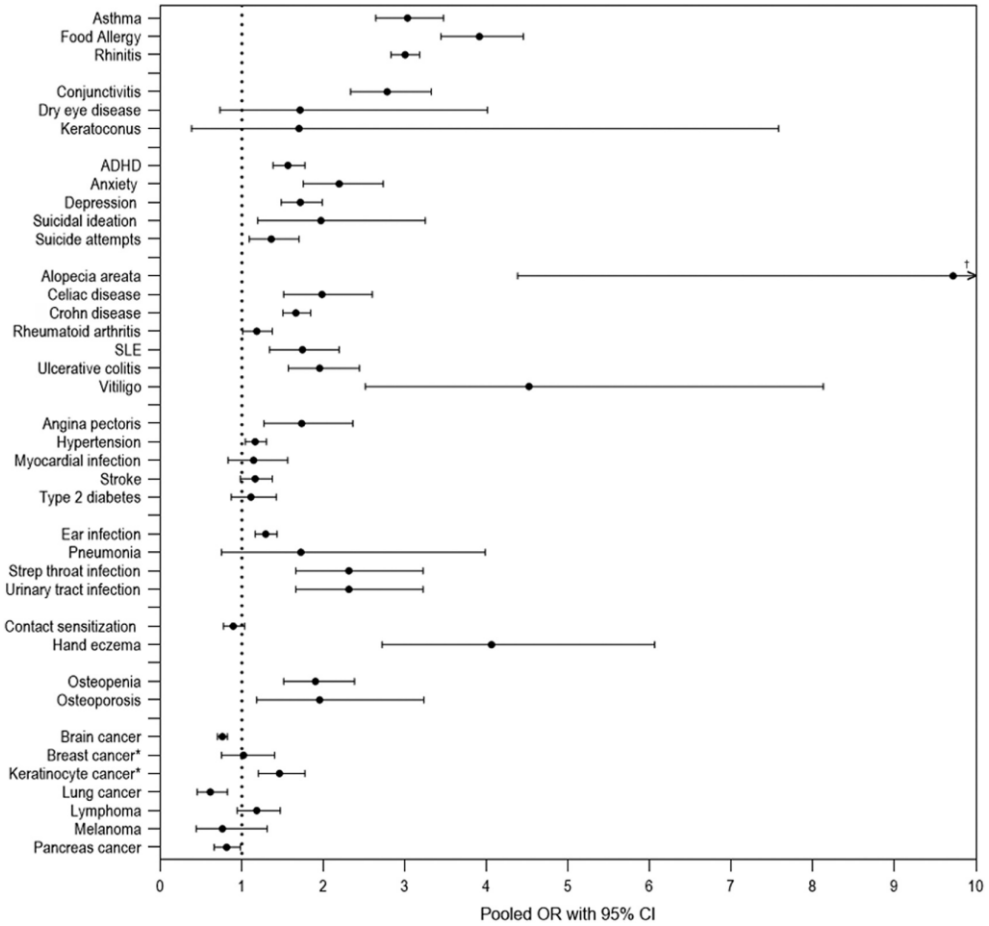
J Allergy Clin Immunol. 2023;151(5):1155-1162. doi:10.1016/j.jaci.2022.12.002
. de Carvalho V, et al. Presented at RAD 2022; 9–11 April 2022; Baltimore, MD, USA.

Ann Allergy Asthma Immunol. 2019;123(2):144-151. doi:10.1016/j.anai.2019.04.020

Outline: Dynamic progression and accumulation of comorbidities in AD

Multisystem comorbidity burden

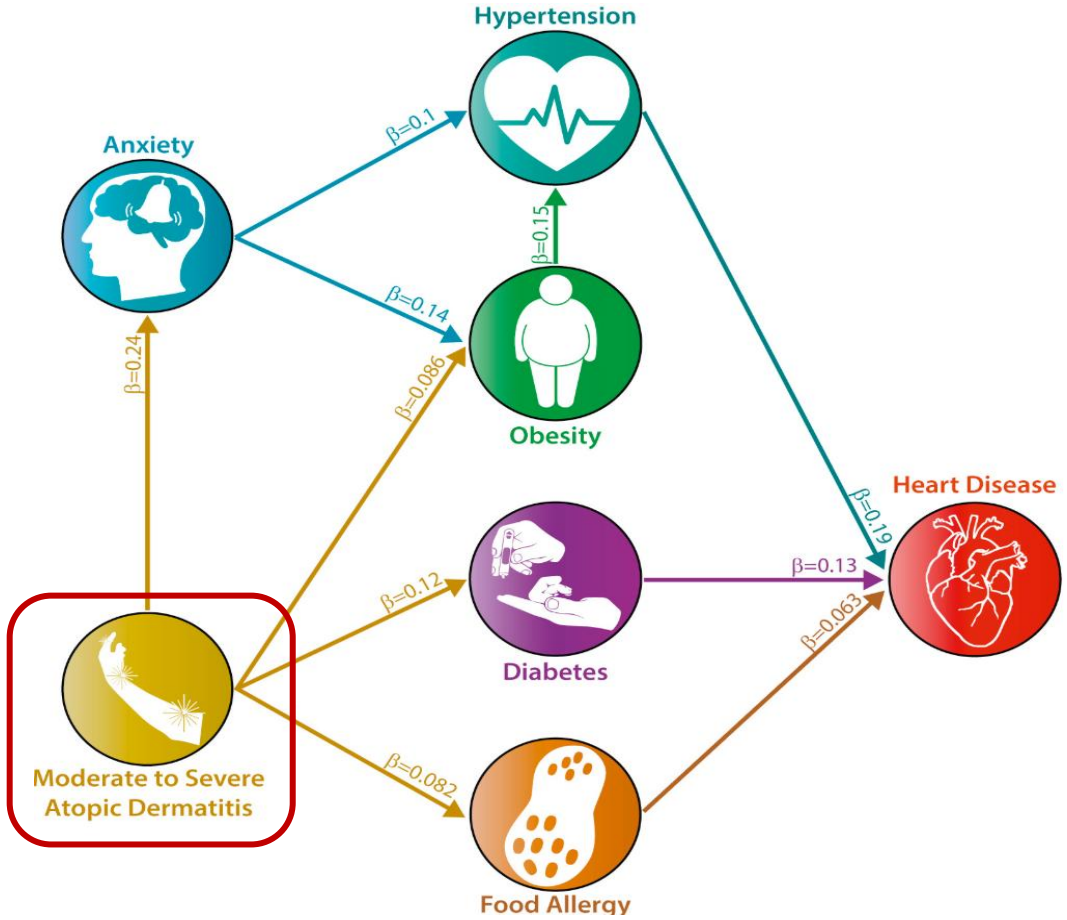
AD was associated with multisystem comorbidities beyond atopic diseases.



Ann Allergy Asthma Immunol. 2019;123(2):144-151. doi:10.1016/j.anai.2019.04.020

Comorbidity progression.

The interactions between comorbidities promote syndemics.



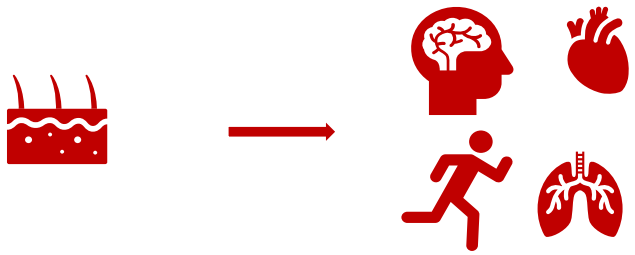
Haddad EB, et al. Dermatol Ther (Heidelb). 2022;12:1501–1533.
Beck LA, et al. JID Innov. 2022;2:100131
Paller AS, et al. Dermatol Ther. 2023;13:961–980.
Neri I, et al. J Asthma Allergy. 2023;16:383–396.
Ramirez FD, et al. Jama Pediatr. 2019:173:e190025.

Wan J, et al. J Allergy Clin Immunol Pract. 2023;11:3123–3132.
Wan J, et al. J Allergy Clin Immunol Pract. 2023:S2213–2198(23)01251
Andersen L, et al. Br J Dermatol. 2020;182:1007–1016.
Henderson AD, et al. BMC Med. 2023;21:285.
Lowe KE, et al. J Allergy Clin Immunol.

Outline

Core Issues We Aim to Address

- Uncover the comorbidity landscape of AD.
- Reveal how the comorbidities sequence, evolve in AD.
- Investigate the clustering patterns of comorbidities and the underlying genetic contributions.
- How different comorbidity impact the treatment.



Study Design and Results

Study Design

中南大学 湘雅医院
XIANGYA HOSPITAL CENTRAL SOUTH UNIVERSITY

Observational study

Identify the diseases associated with atopic dermatitis

Data source

Medical record

Primary care, hospital record, death registory data.
The diagnoses of diseases were mapped to phecode system.

Exposure

Diagnosis of atopic dermatitis was based on selected ICD codes: L208, L209, L20, L309, 6918, 69180, and 6929

Outcome

Outcome determination was based on ICD-10 codes and mapped to 1,429 phecodes.

Sample matching

11,065 individuals with atopic dermatitis — 1:10 age, sex TDI matched → 110,650 individuals without atopic dermatitis

Statistial analysis

Conditional proportional hazard model

The incidence of 1,429 phecode-defined outcomes

Outcome events, Death, Loss or end of follow up.

Baseline — Follow up — Endpoints

Disease outcomes associated with atopic dermatitis

Map the trajectory of comorbidities in individuals with atopic dermatitis

Step 1: Explore comorbidity trajectory and clusters.

Comorbidity Strength	Magnitude of Association	Temporal Relationship
Relative risk and Pearson correlation (Phi-coeffecient)	Risk set sampling and conditional logistic regression	Binomial test
Co-occurring Pairs	Comoridity network	Temporal trajectory

Comorbidities with intrinsic connections ↔ Clustering Anlysis → Trajectories of comorbidities within each clsuter

Step 2: Explore the genetic determinants of clusters.

Disese clusters

Infectious, Skin-gut, Mental, Cardiometabolic, Musculoskeletal

Calculate the number of diseases in each cluster for each individual

Genotyping array data

Quality control of genetic-level and individual-level

Cluster-specific score ← GWAS → Genetic data

Annotation through FUMA

IndSigSNPs → Mapped genes → Pathway

Through SNP2GENE and MAGMA

Genetic analysis

Provide insights from genetic perspective

PRS-PheWAS

The disease outcomes associated with the PRS of atopic dermatitis.

Logistic regression

LDSC

The genetic linkage between atopic dermatitis and disease outcomes

genetic correlation

Two sample MR

The genetic casual evidence between atopic dermatitis and 2469 diseases from FinnGen data.

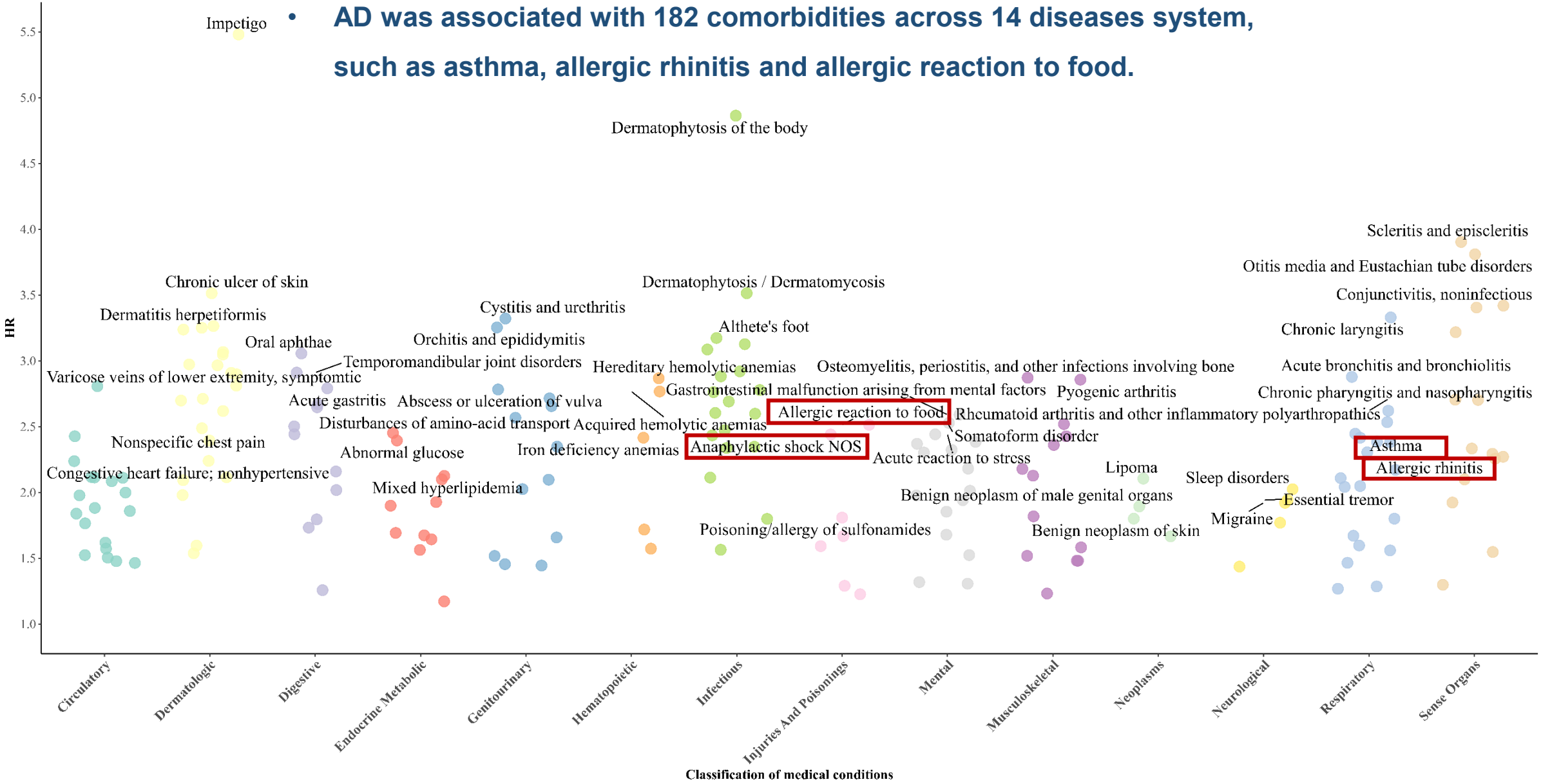
casual relationship

Research Question 1:

The Comorbidity profile in AD.

Research Question 1: The Comorbidity Profile of of AD.

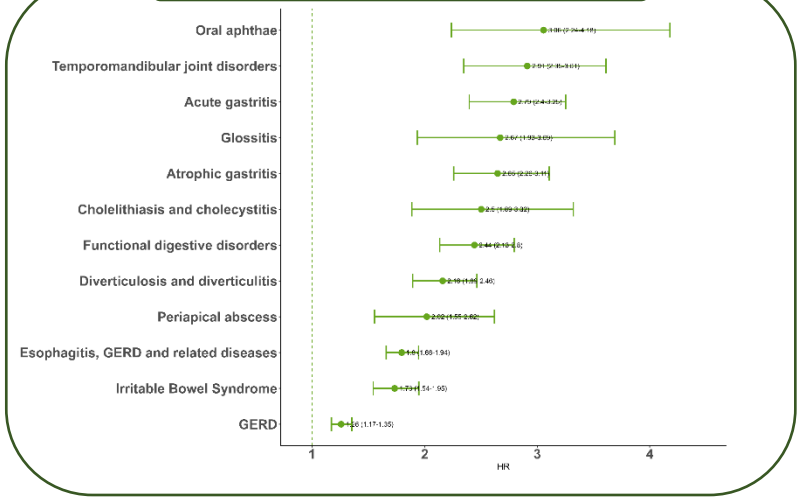
- **AD was associated with 182 comorbidities across 14 diseases system, such as asthma, allergic rhinitis and allergic reaction to food.**



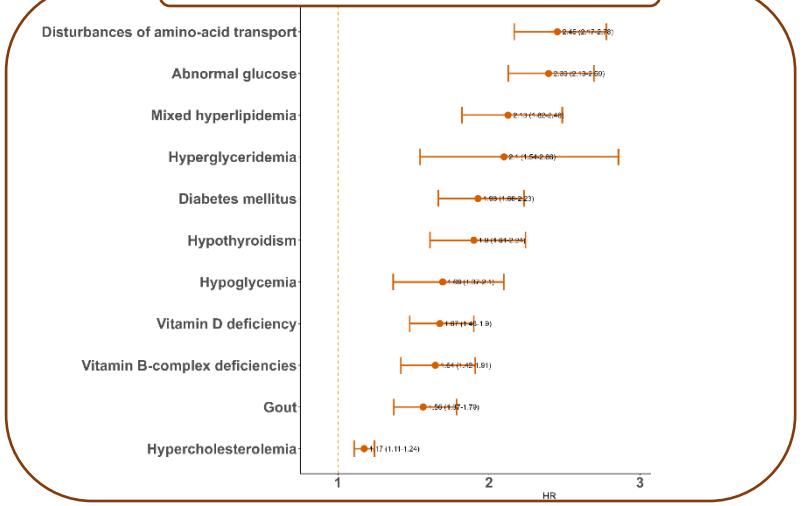
Research Question 1: The Comorbidity Profile of of AD.

AD is associated with an increased risk of **multisystem** diseases, extending **beyond atopic comorbidities and cutaneous conditions.**

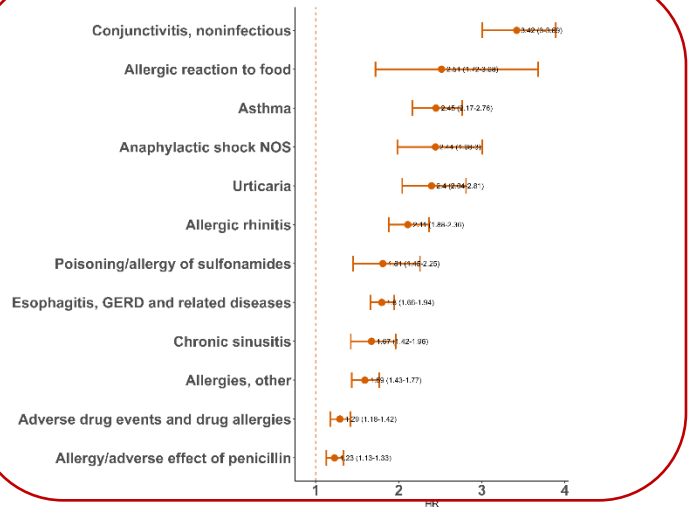
Digestive



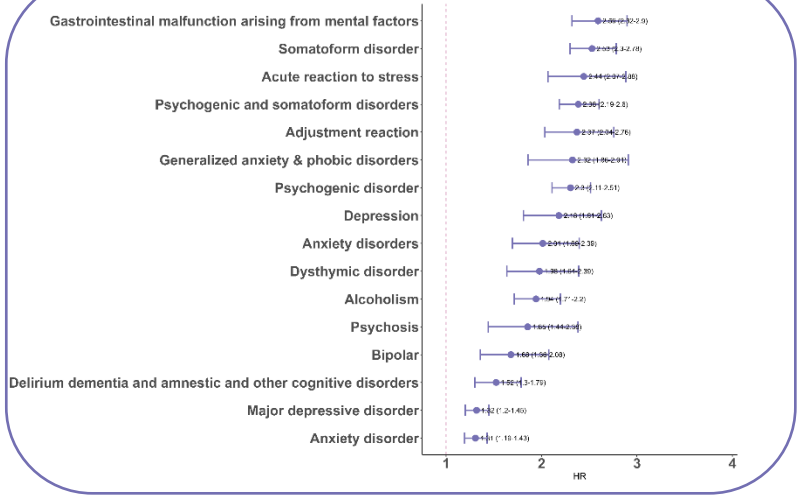
Endocrine



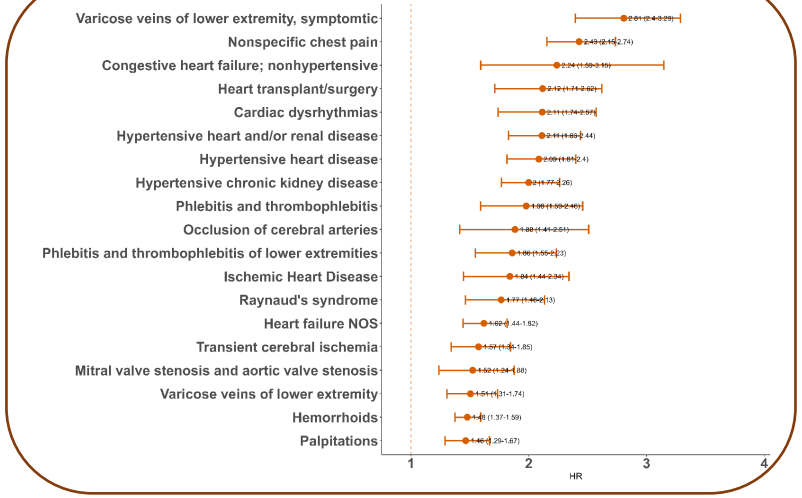
Atopic



Mental

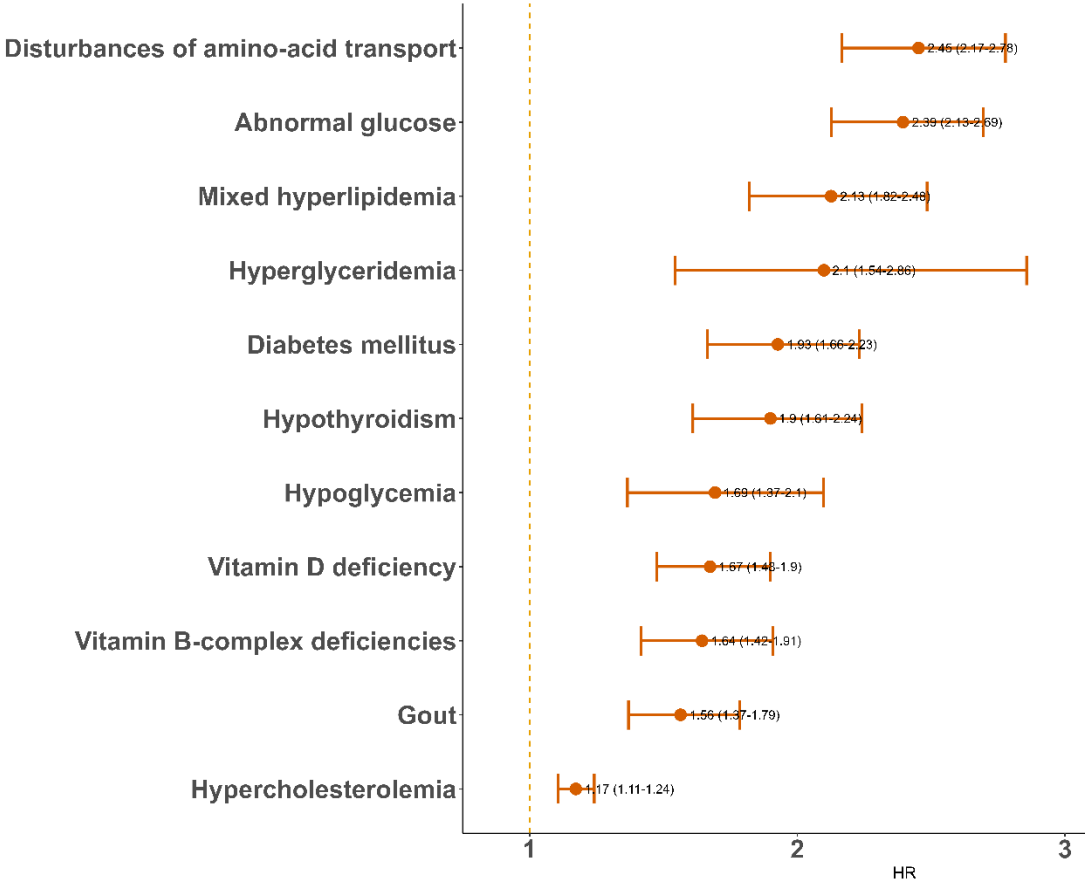


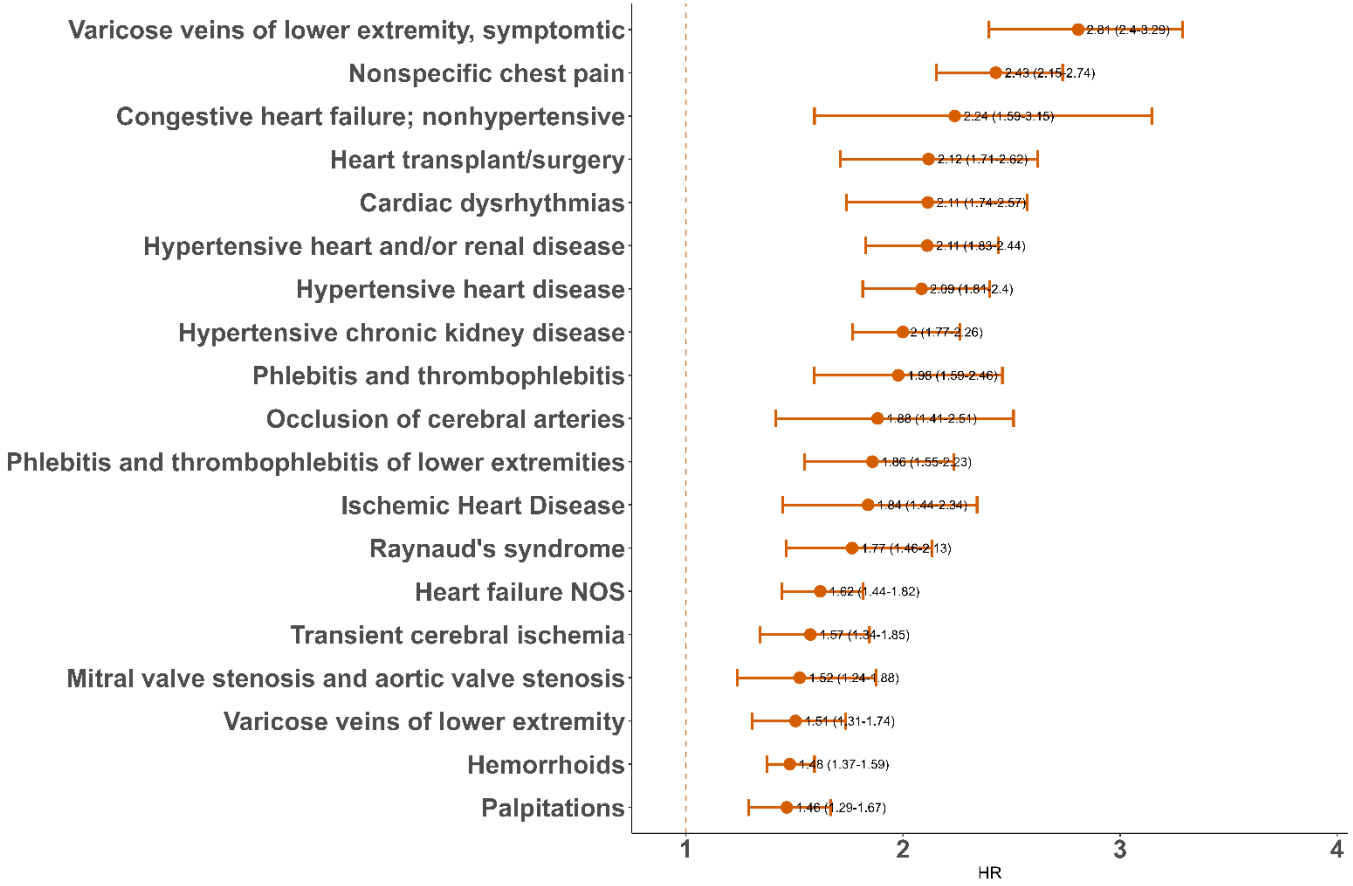
Circulatory



Results 1: The comorbidity spectrum of AD

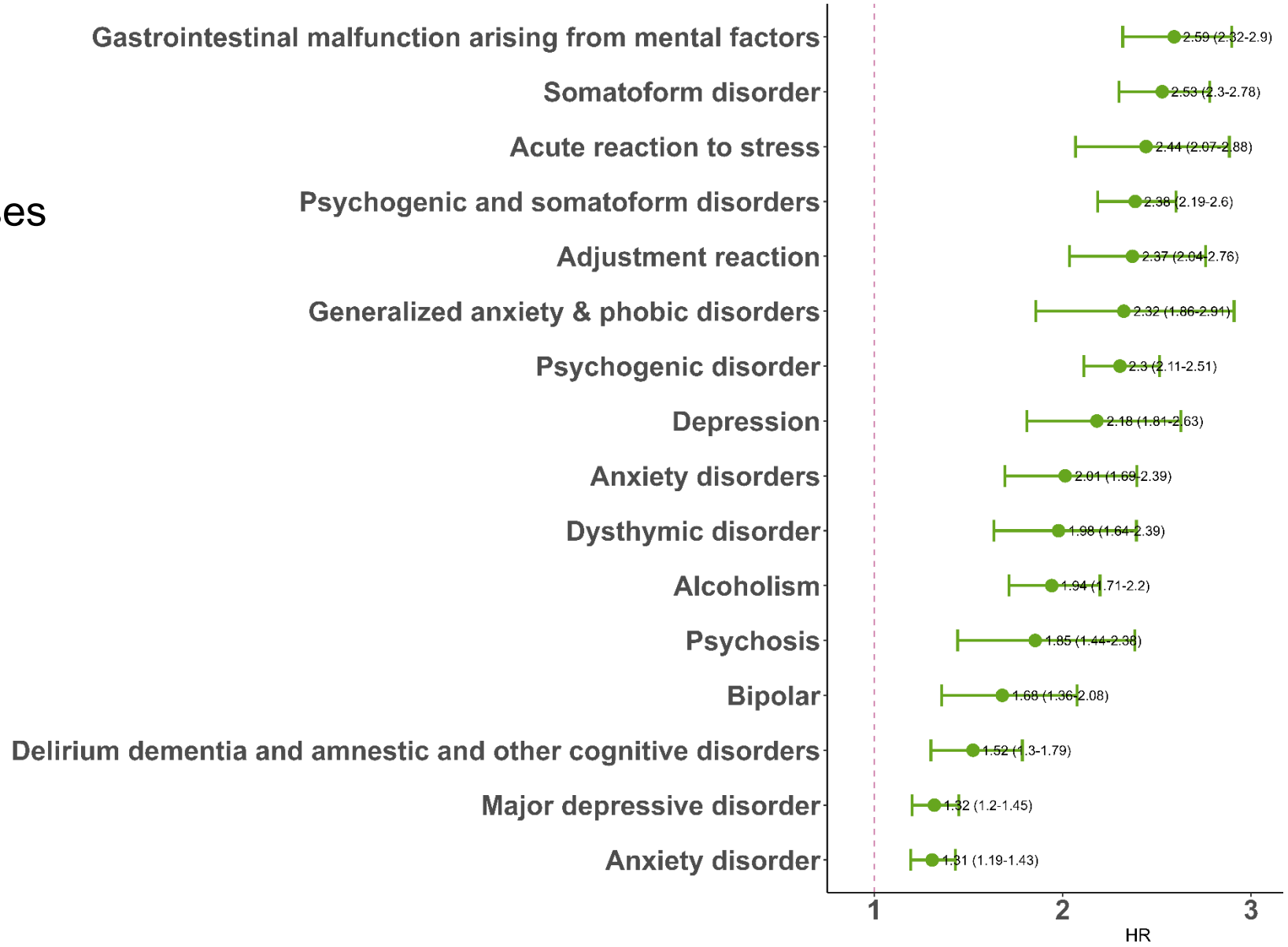
Many cardiometabolic diseases were associated with AD, including glucose and lipid disorder, cardiac dysrhythmias and heart failure.





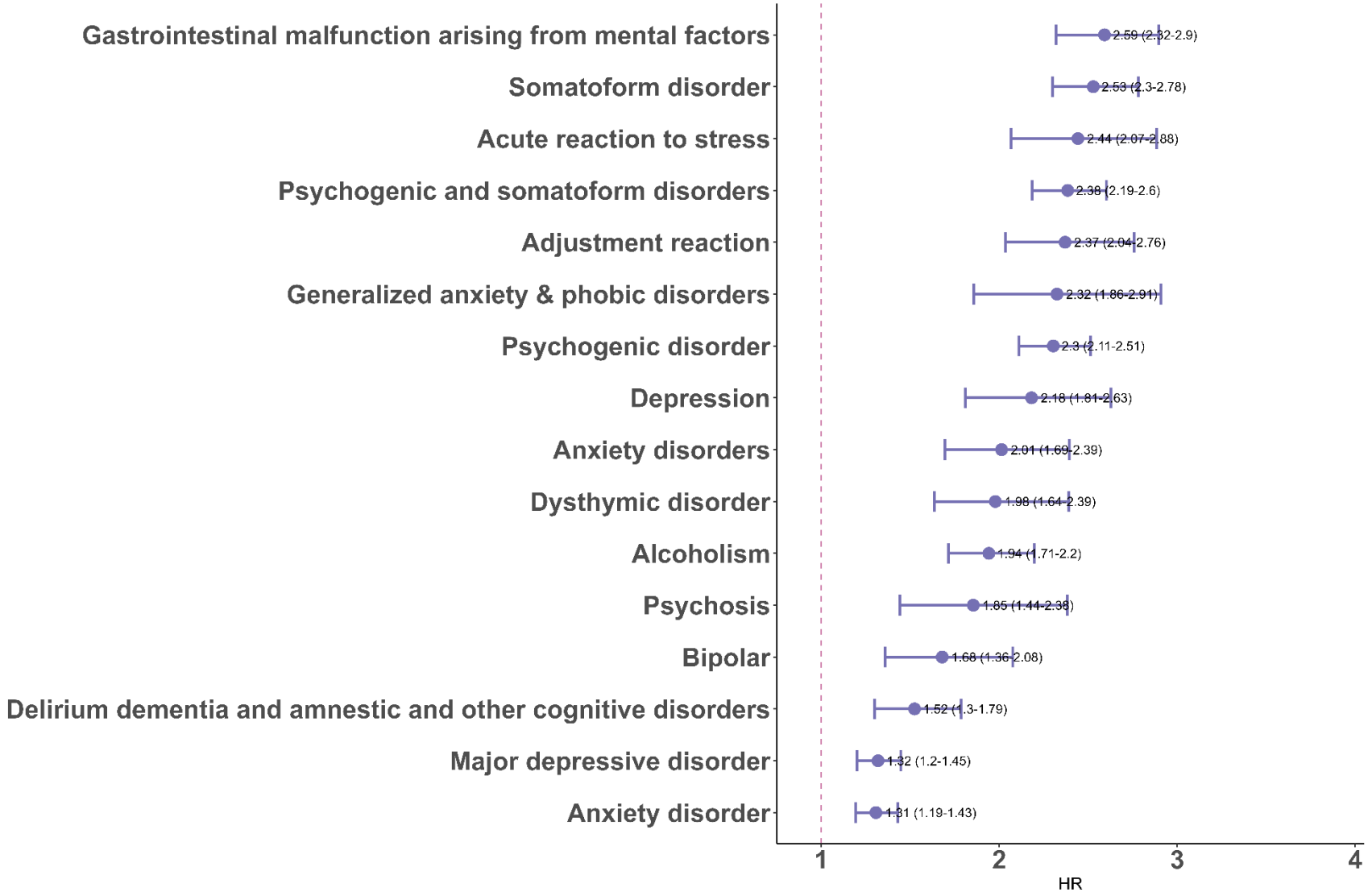
Results 1: The comorbidity spectrum of AD

Digestive functional disorders, gastroenteritis and ulcers diseases are also associated with AD.



Results 1: The comorbidity spectrum of AD

Diverse mental disorders were associated with AD, including acute reaction to stress, depression, anxiety and bipolar.



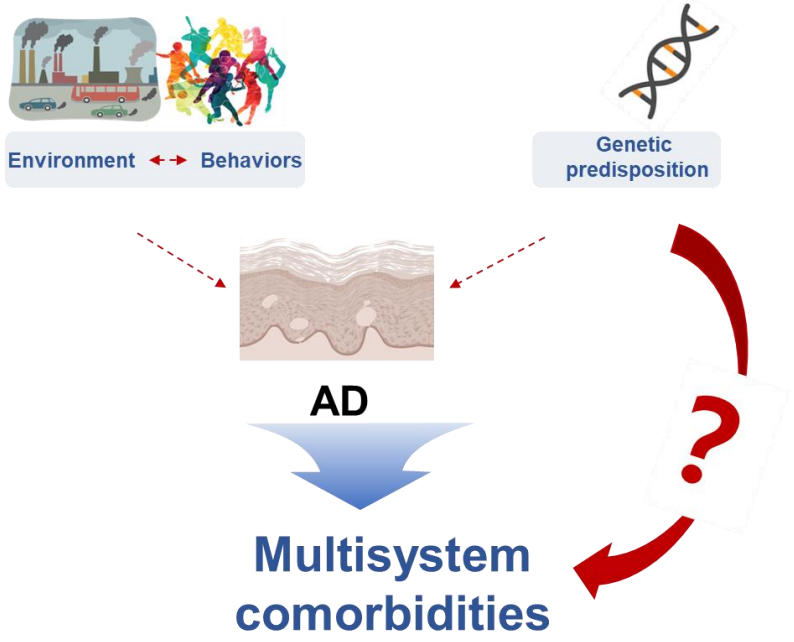
Research Question 2:

How the genetic predisposition influence the comorbidities

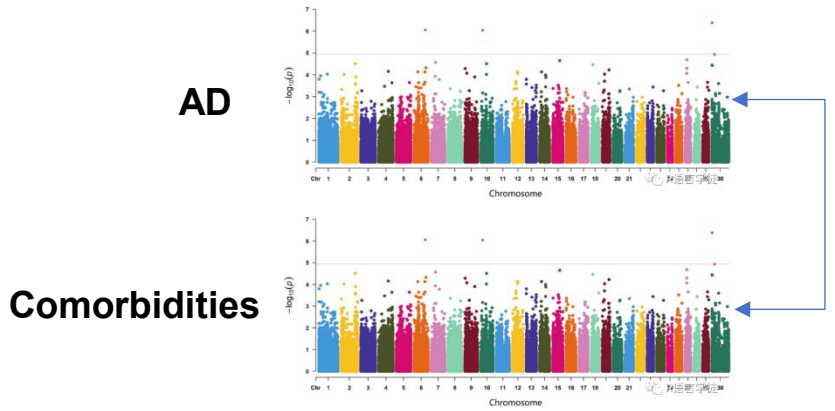
Research Question 2: Genetic Relationship Between AD and Comorbidities

We conducted PRS-PheWAS, LDSC and two-sample Mendelian Randomization PheWAS.

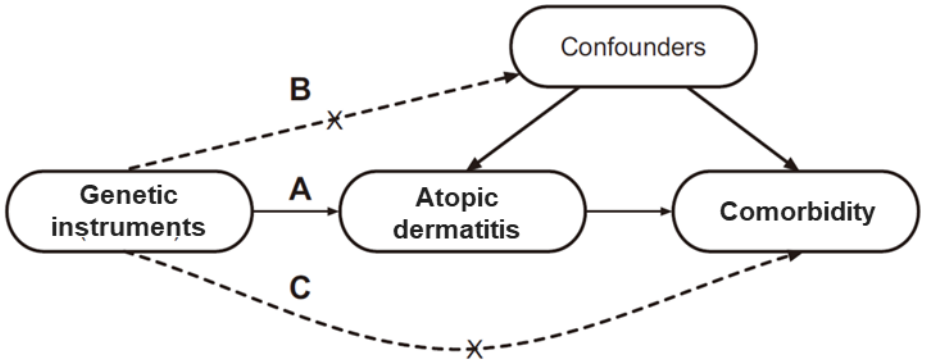
PRS-PheWAS



LDSC



TSMR-PheWAS

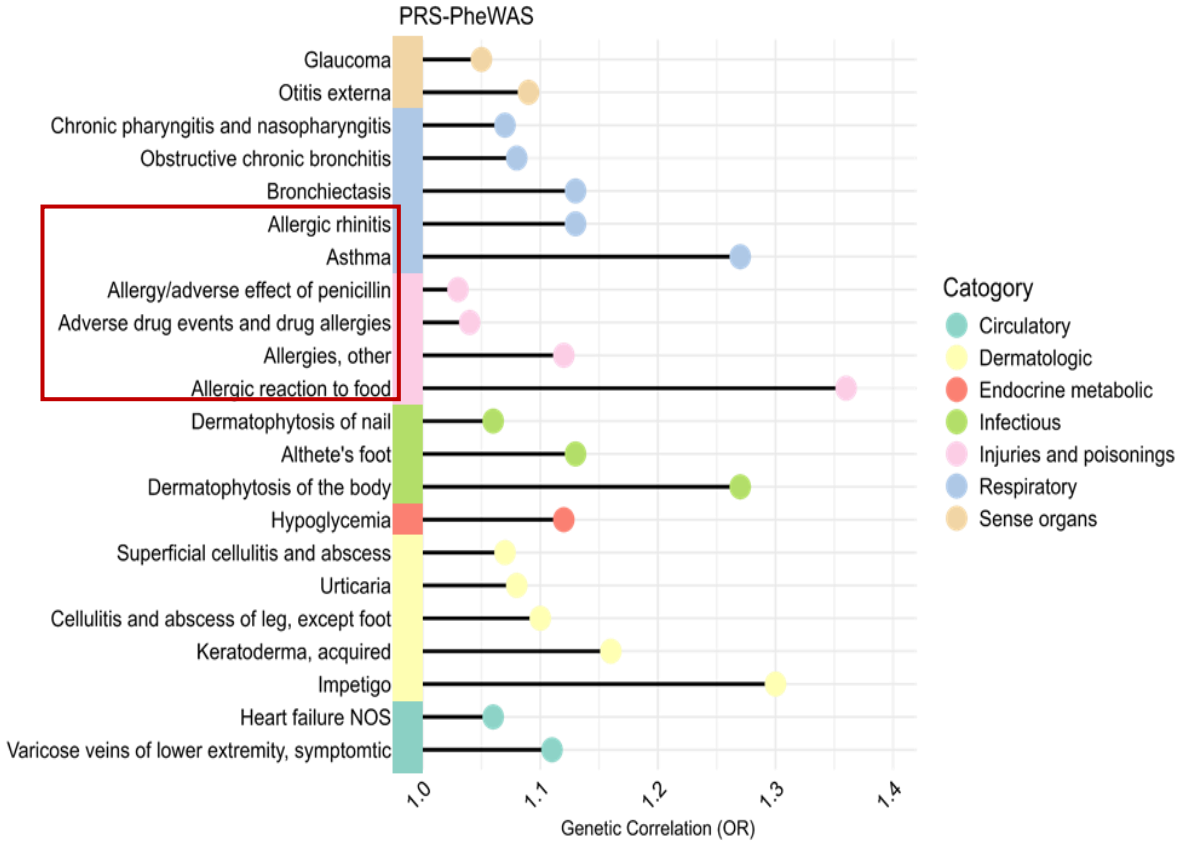


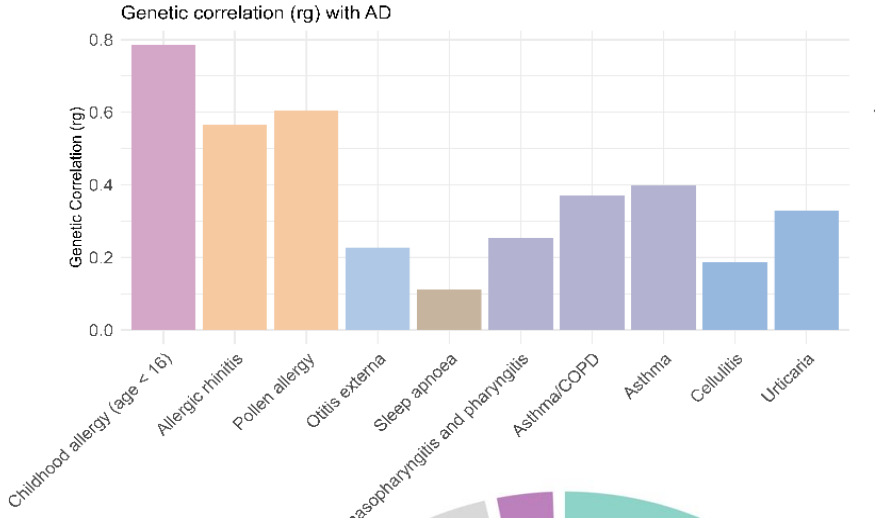
In submission 2025

Results 2: Genetic analysis

Significant correlation:

- Asthma, allergic rhinitis, urticaria and drug allergies.
- Infections in different system.





Results 3: Trajectory and clustering analysis

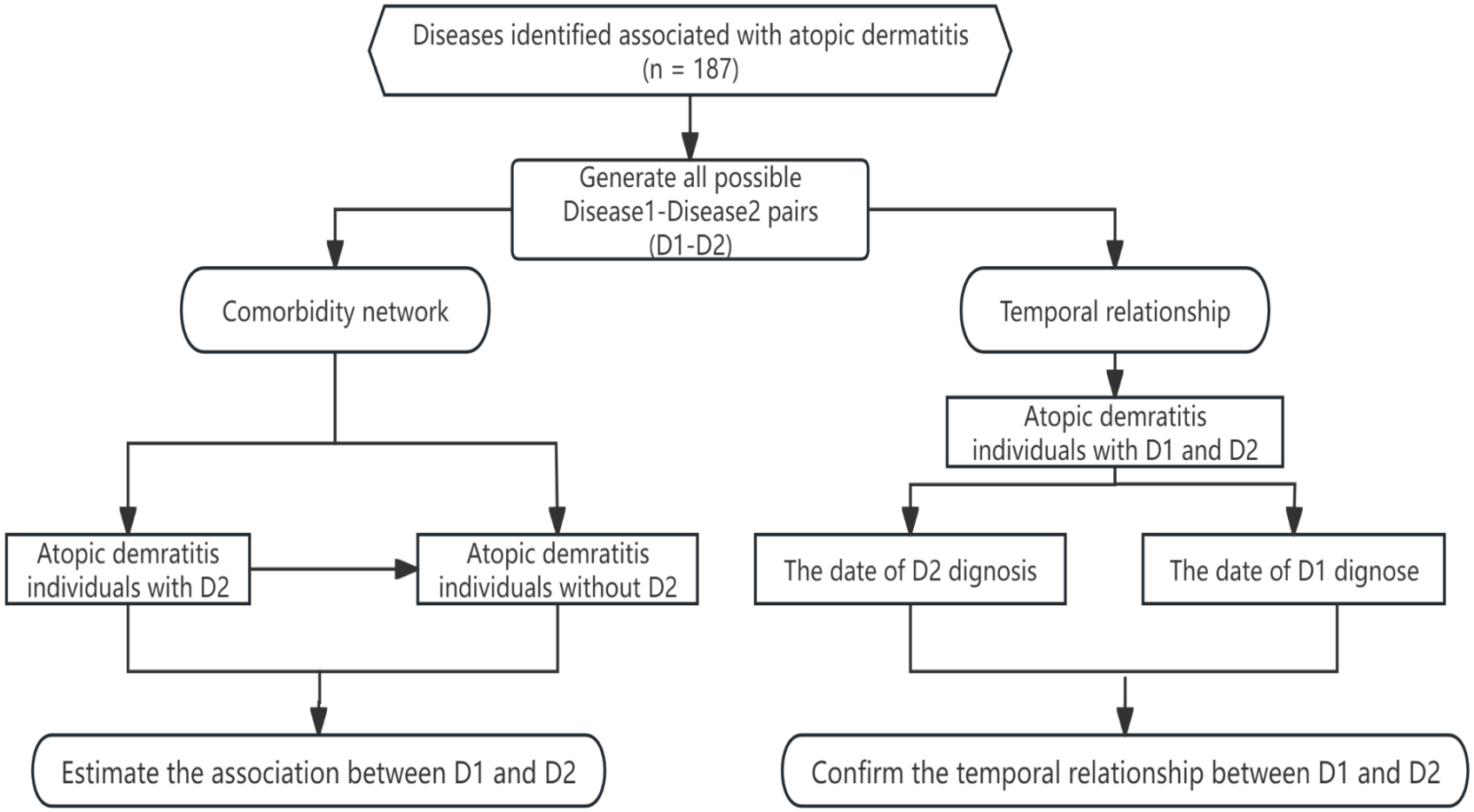
- **Scientific question 3:**
  - **How the comorbidities sequence, evolve to form temporal trajectory?**
  - **How the comorbidities diverged to clusters and the genetic contributions?**

Results 3: Trajectory and clustering analysis

Ensure the comorbidity strength
Relative risk (RR) and Pearson's correlation (Φ-correlation) were calculated for each disease pair.

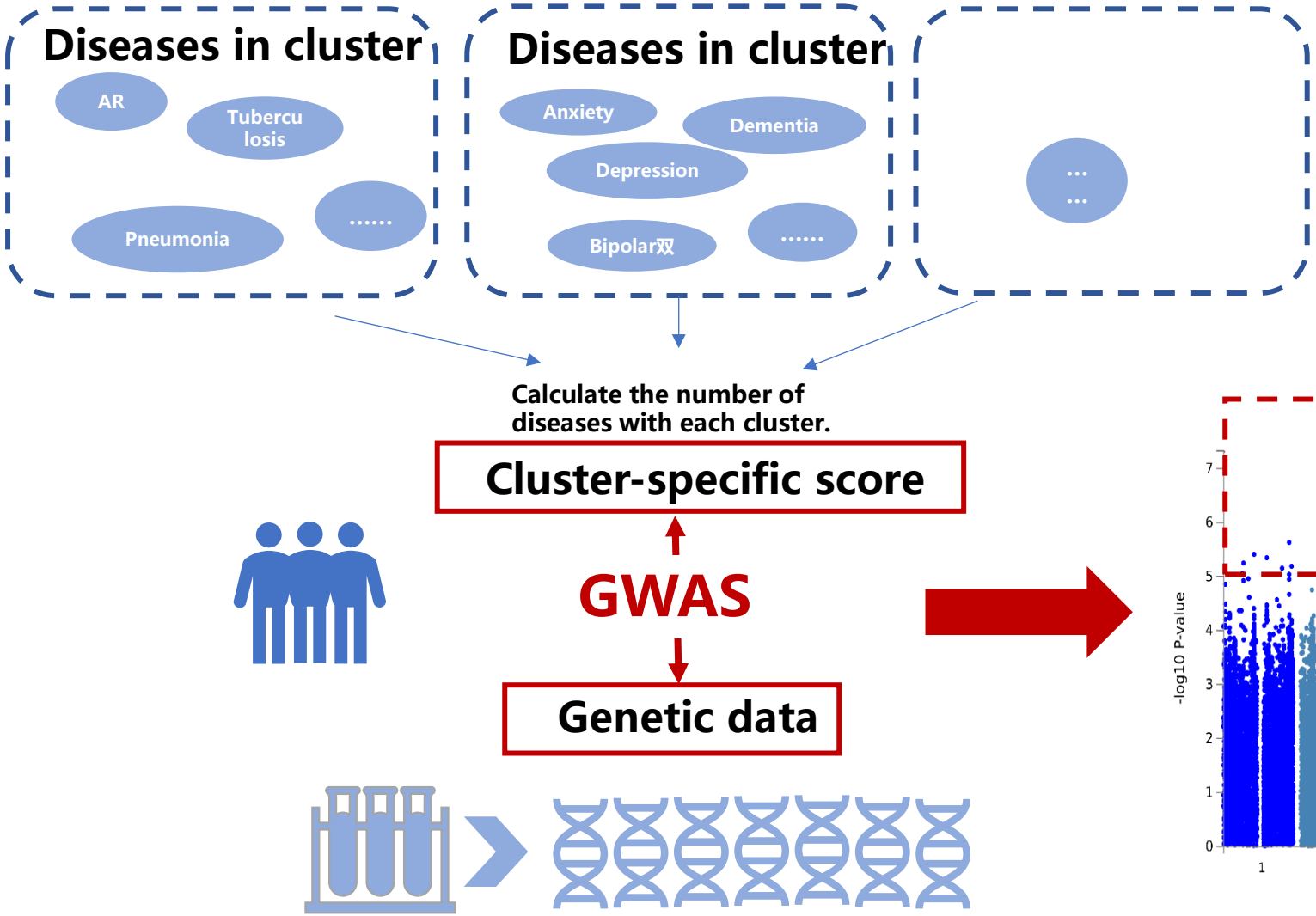
Confirm chronological model
Binomial tests were utilized to identify the sequential order of Diseases1 and Disease2

Identify the strength of associations
Conditional logistic regressions were conduct to estimate the association between Disease1 and Disease2



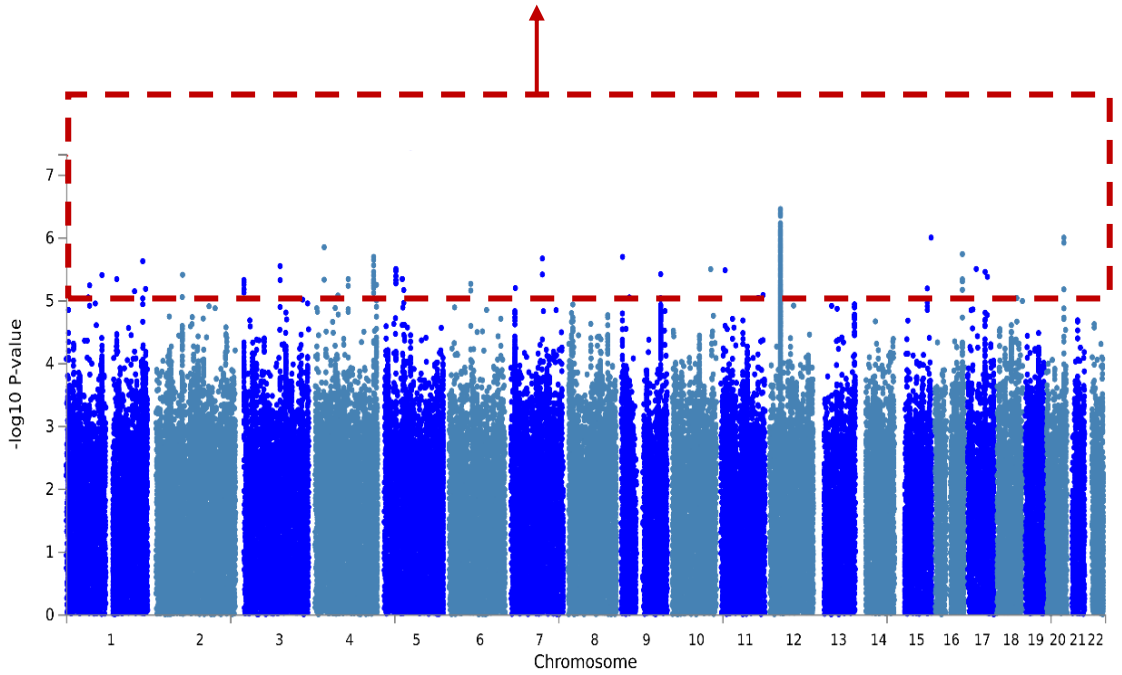
Results 3: Trajectory and clustering analysis

The genetic contributors underlying each cluster.



Enriched pathways with each cluster.

The significant SNPs mapped genes.



In submission 2025

Results 3: Trajectory and clustering analysis

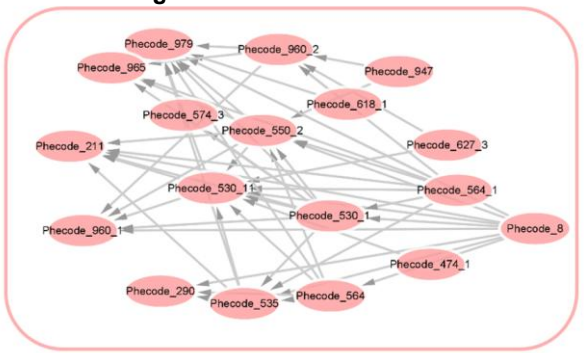
3,526 disease pairs

Louvain identified **5** clusters

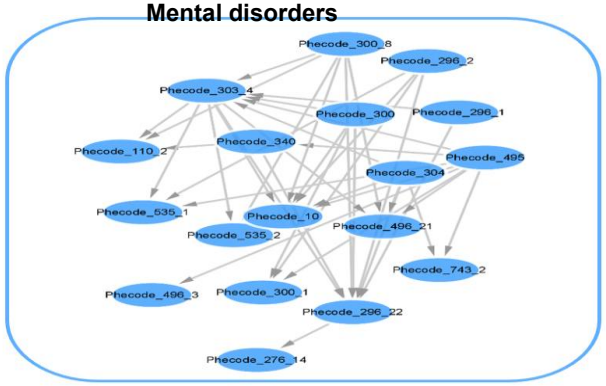
954 pairs with chorological relationships

AD

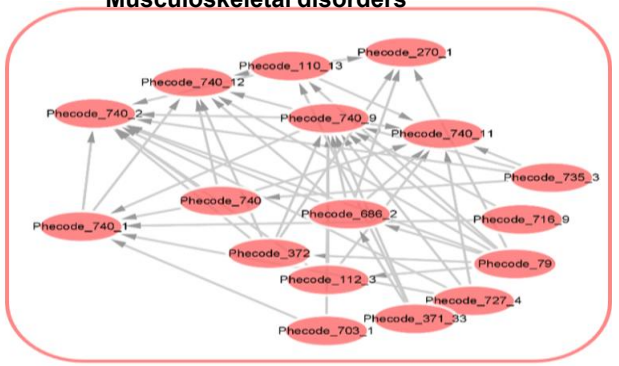
Skin – gut diseases



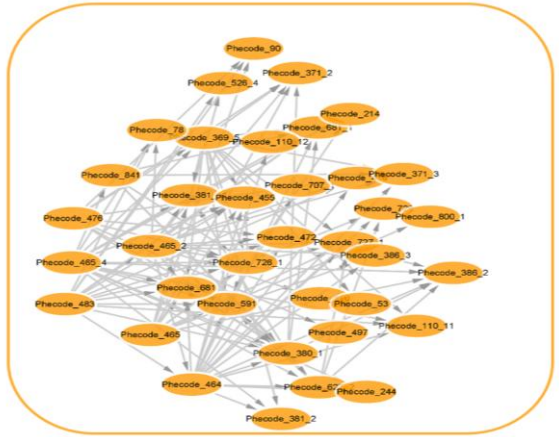
Mental disorders



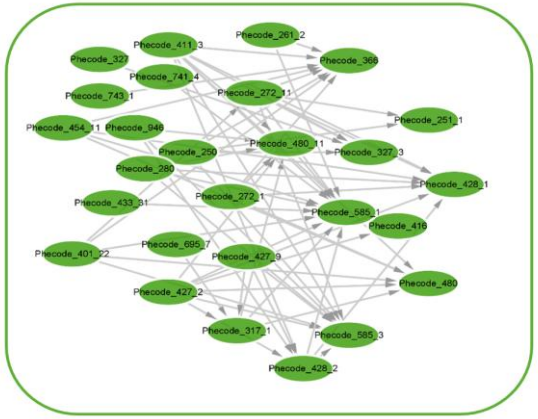
Musculoskeletal disorders



Infectious disease



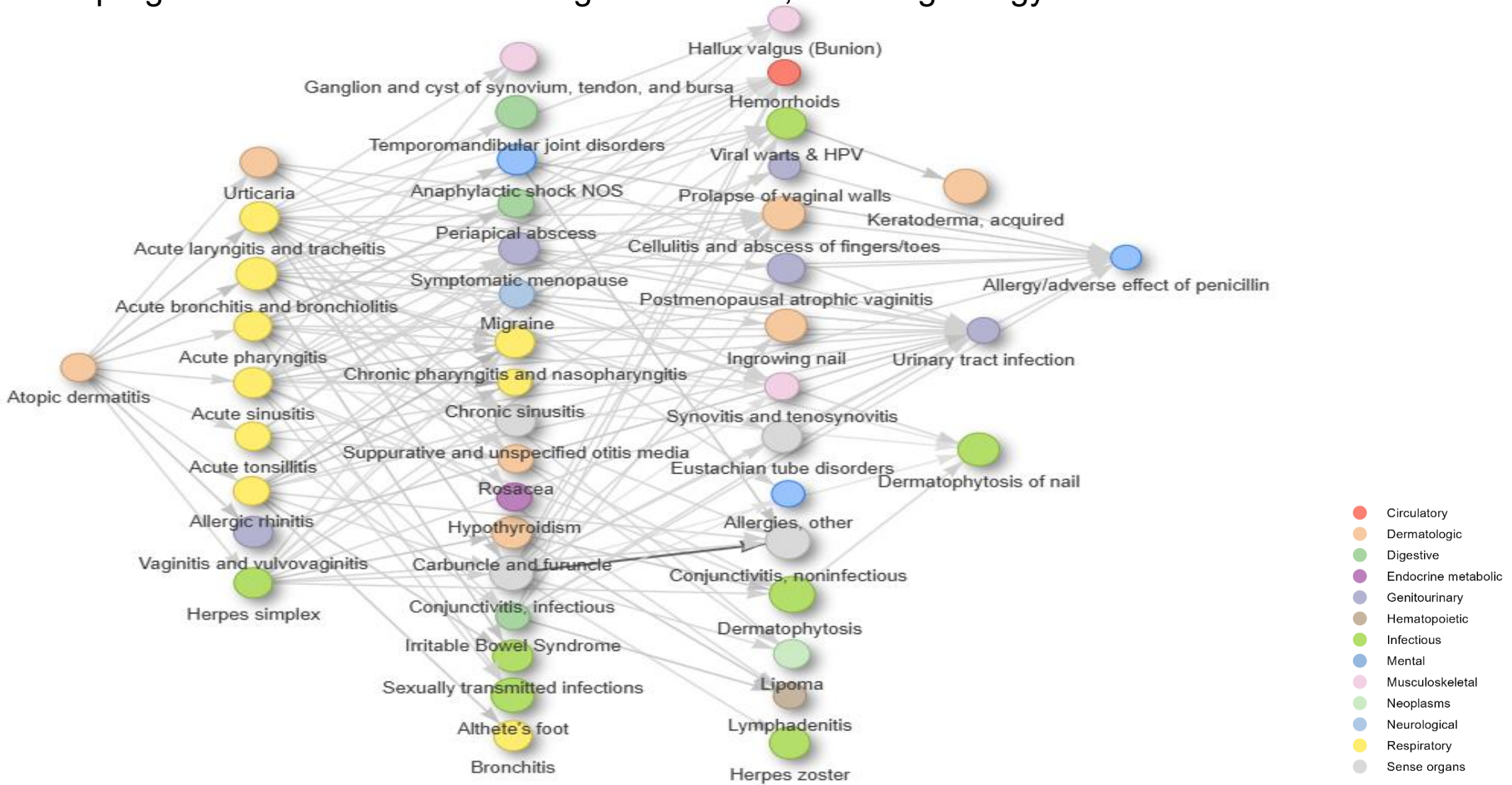
Cardiometabolic disease



Results 3: Trajectory and clustering analysis

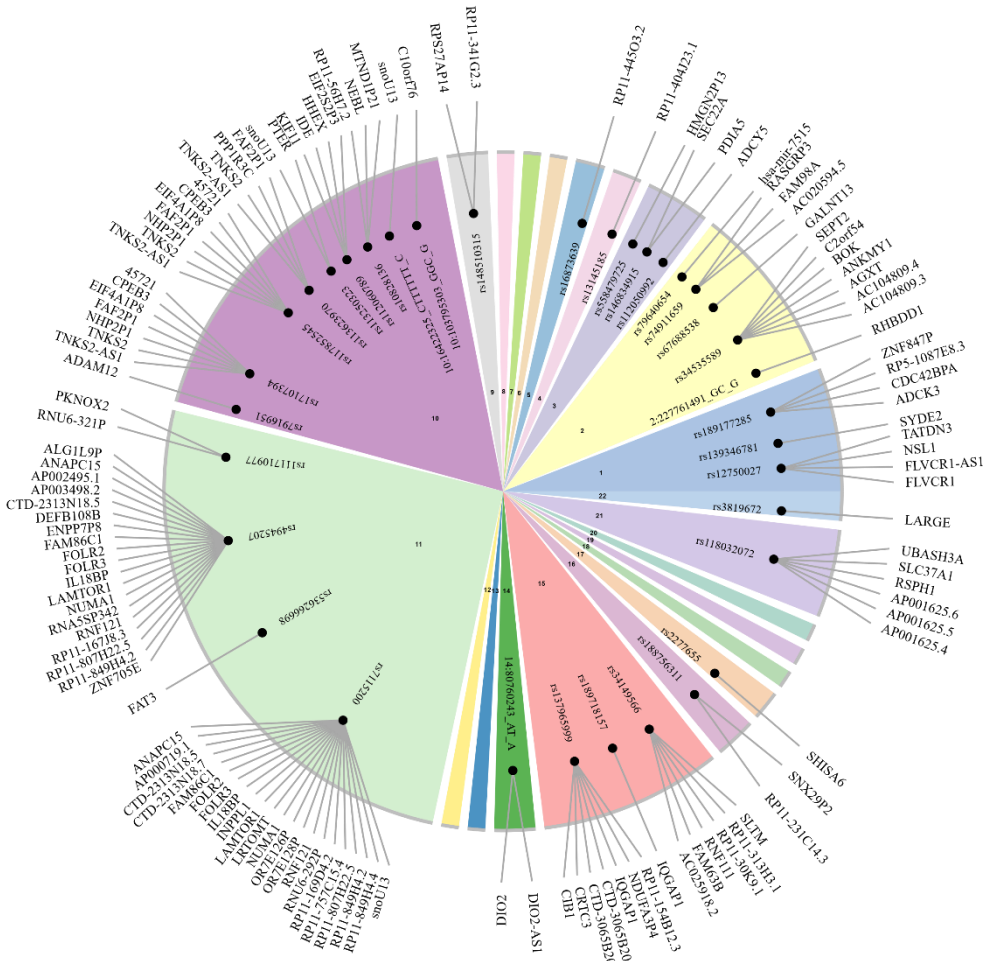
Atopic and infectious cluster

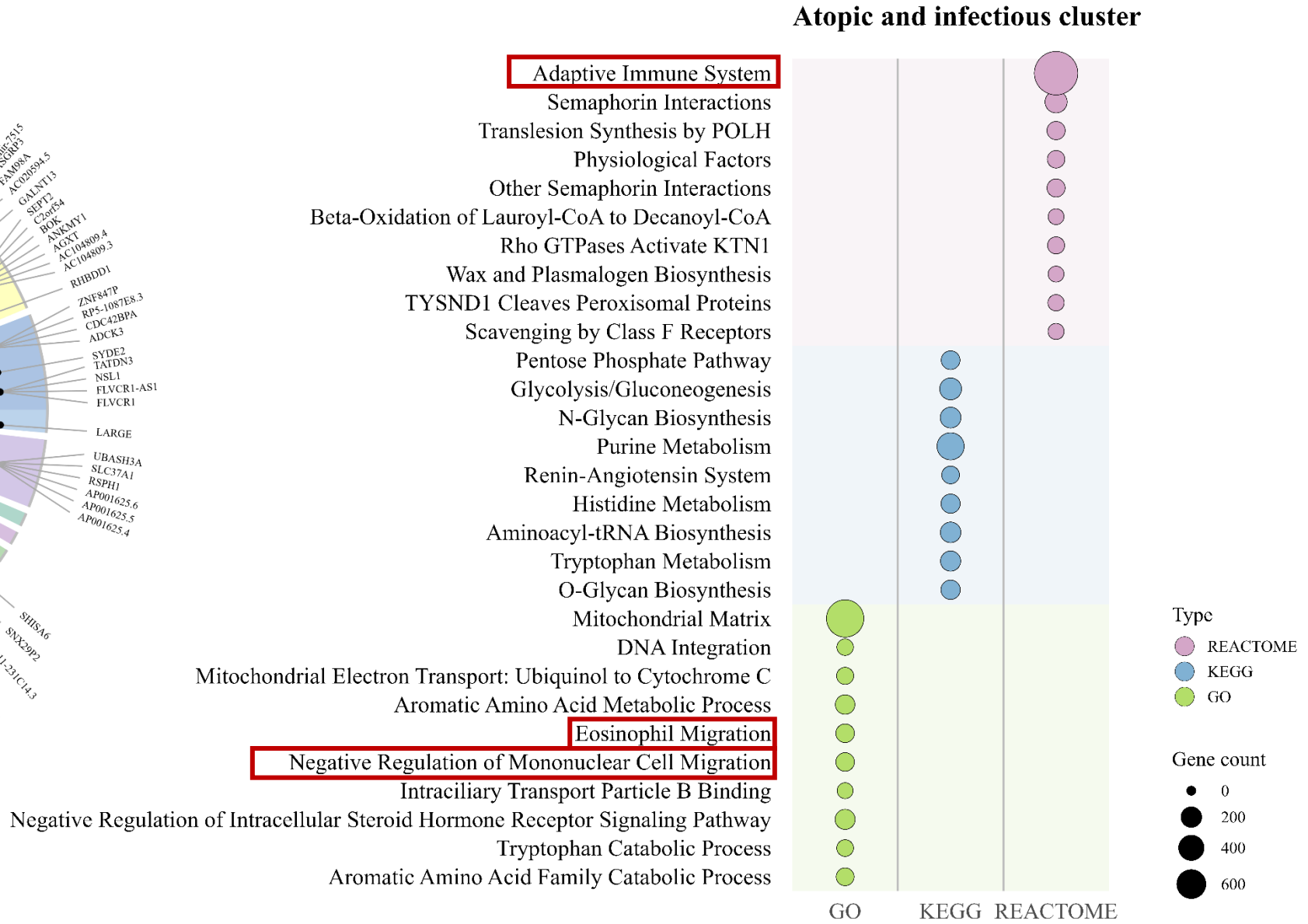
This cluster start with AR, urticaria, and acute respiratory infections, subsequently progress to chronic and multi-organ infections, and drug allergy.



Results 3: Trajectory and clustering analysis

Increased eosinophil migration decreased mononuclear cell and were enriched.

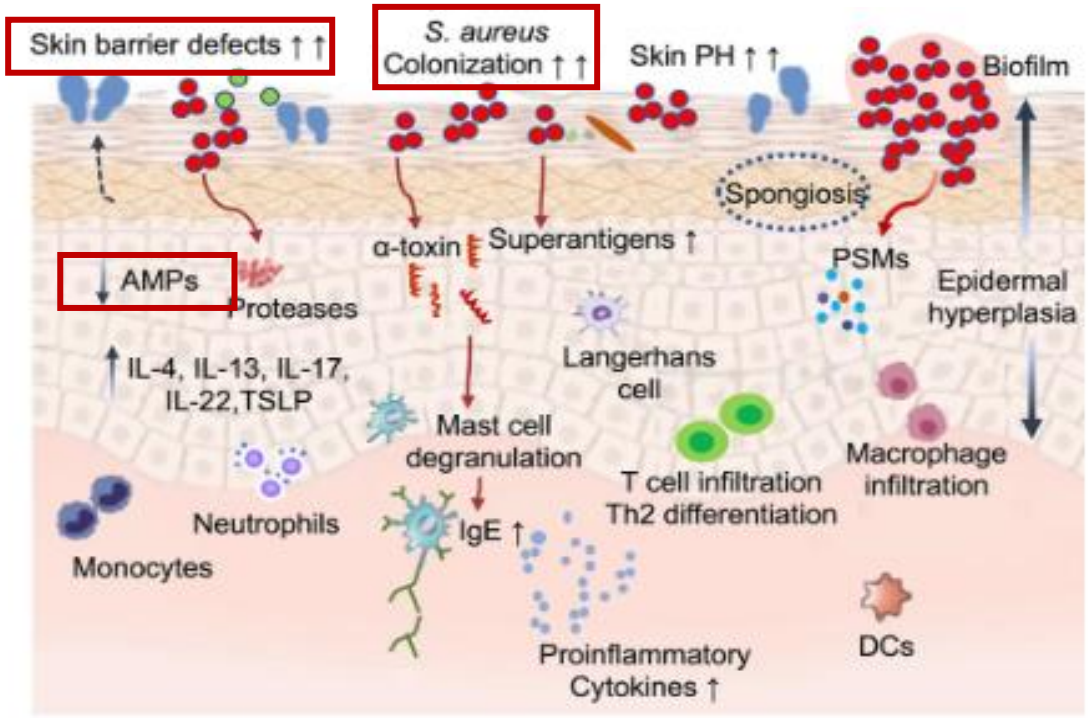


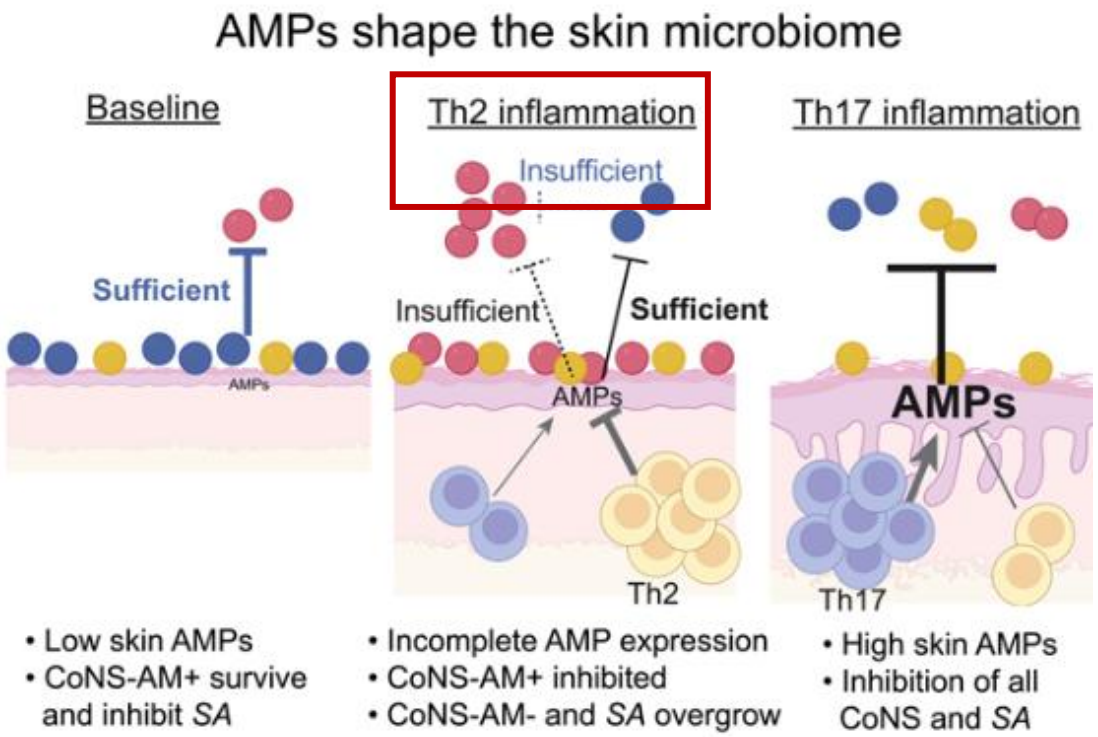


Clin Rev Allergy Immunol. 2016 Dec;51(3):329-337

Results 3: Trajectory and clustering analysis

Th2 immune activation often leads to barrier dysfunction, pH shifts, thereby increasing susceptibility to infection.



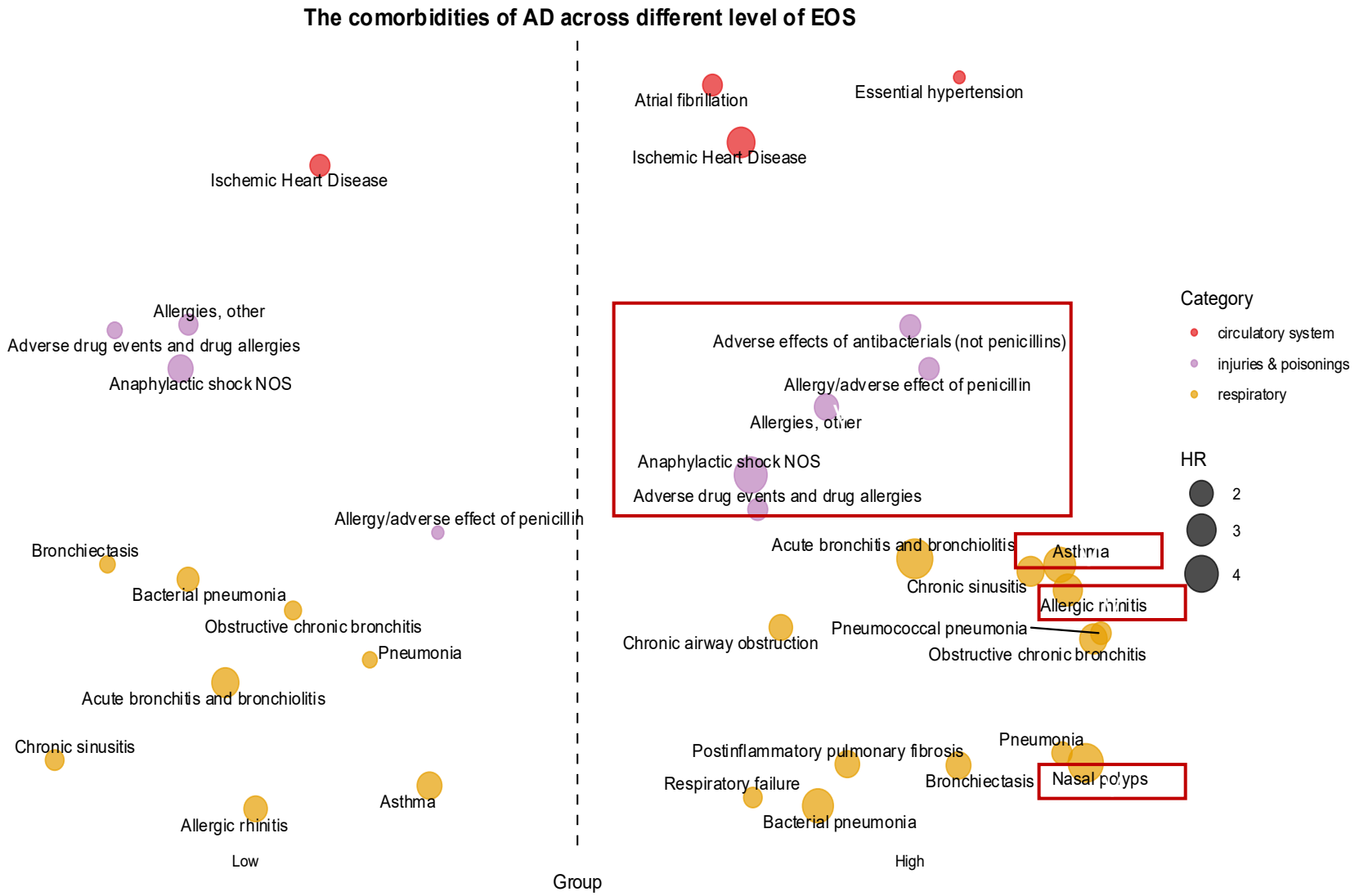


For individuals with this comorbidity cluster, biologic agents targeting the Th2 related pathway may improve clinical prognosis.

J Allergy Clin Immunol. 2014 Aug;134(2):247-57; Clin Exp Immunol. 2000;122:16–9; Curr Treat Options Allergy 12, 3 (2025) Cell Mol Immunol. 2025 Mar;22(3); Cell Rep. 2023 May 30;42(5):112494;

Results 3: Trajectory and clustering analysis

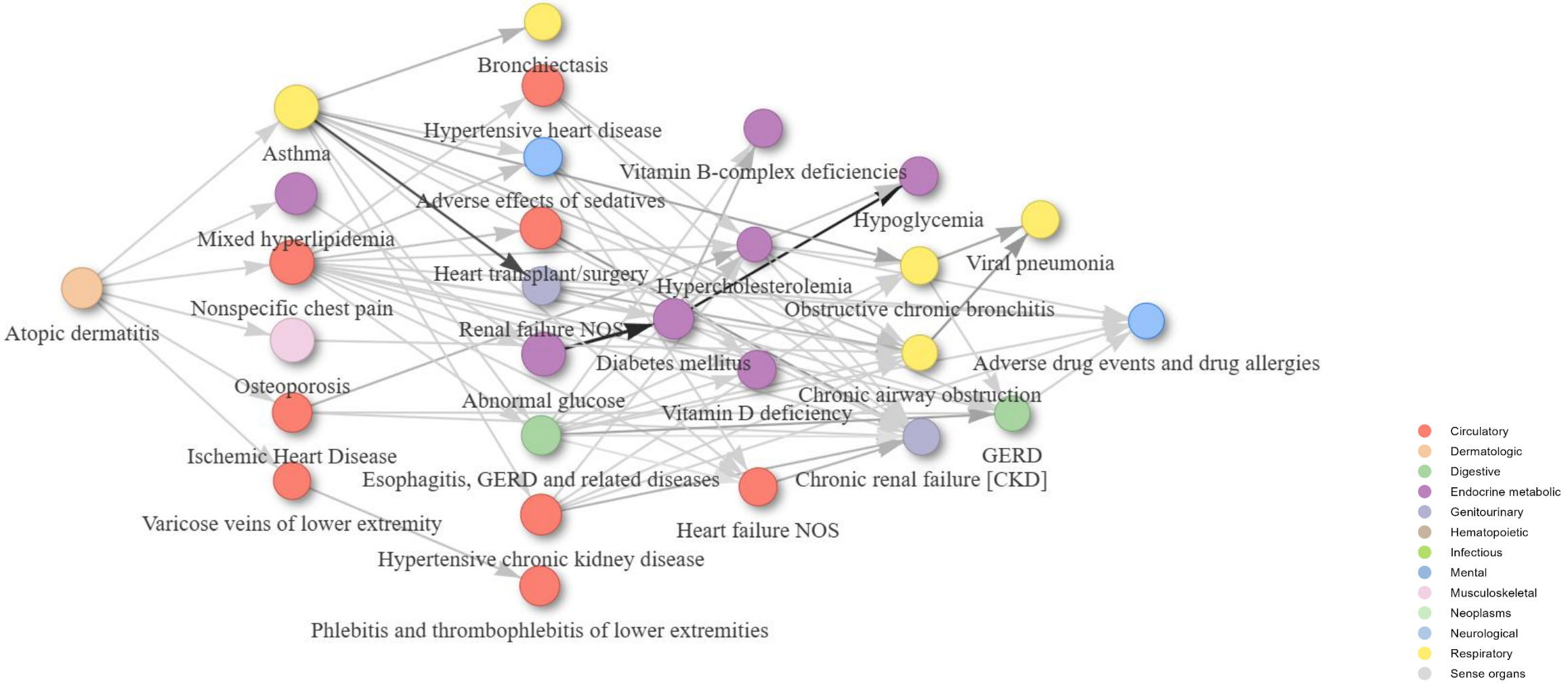
AD with high eosinophil level had higher risk of atopic and infectious diseases.



Results 3: Trajectory and clustering analysis

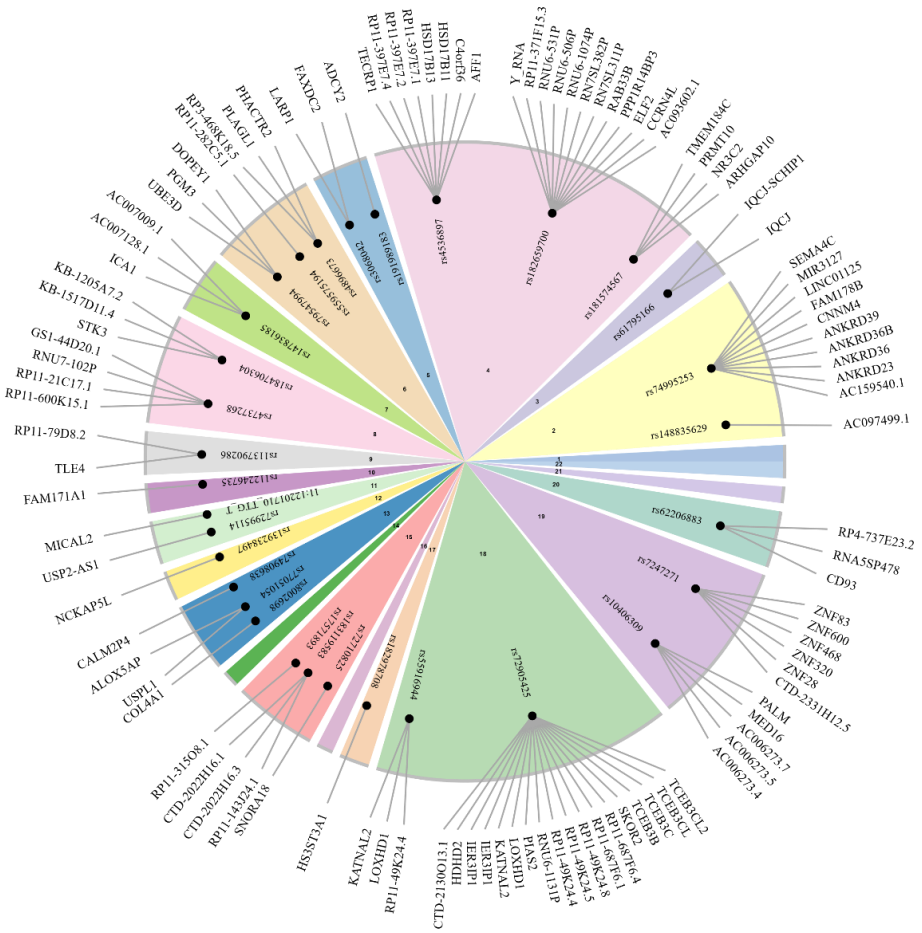
Cardiometabolic disorders

The cardiometabolic cluster characterized by glucose-lipid dysregulation, and ischemic heart disease, ultimately progressing to heart and renal failure.

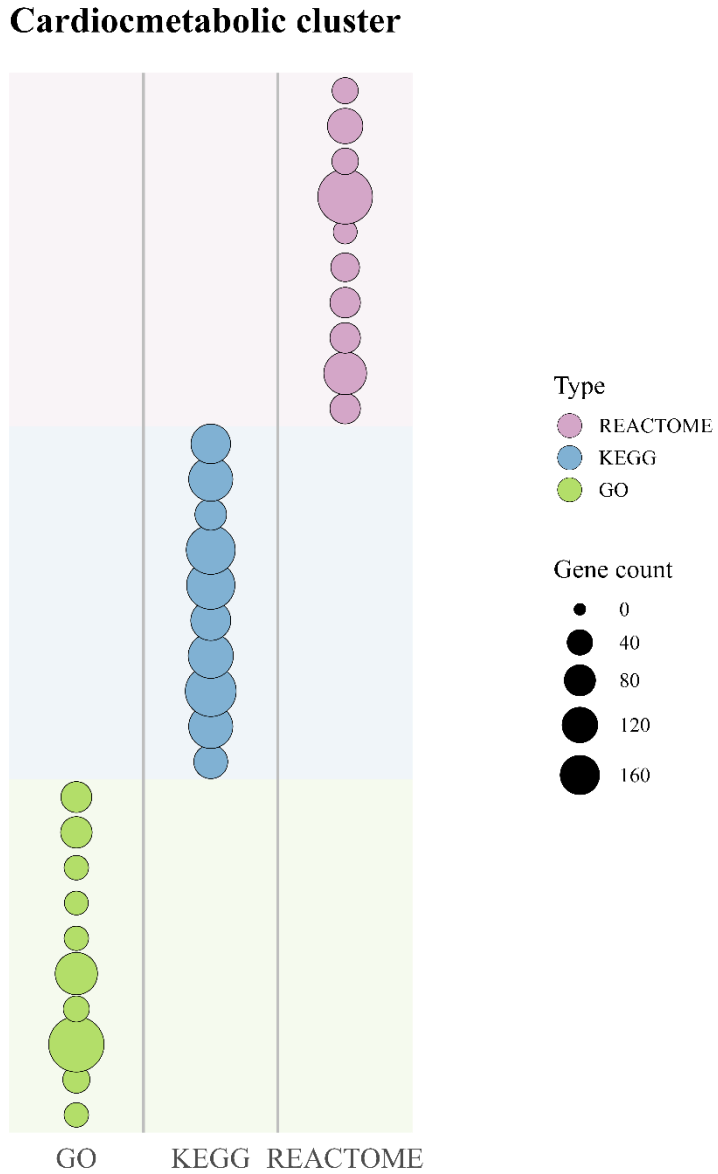


Results 3: Trajectory and clustering analysis

Fatty acid, senescence were enriched in this cluster.

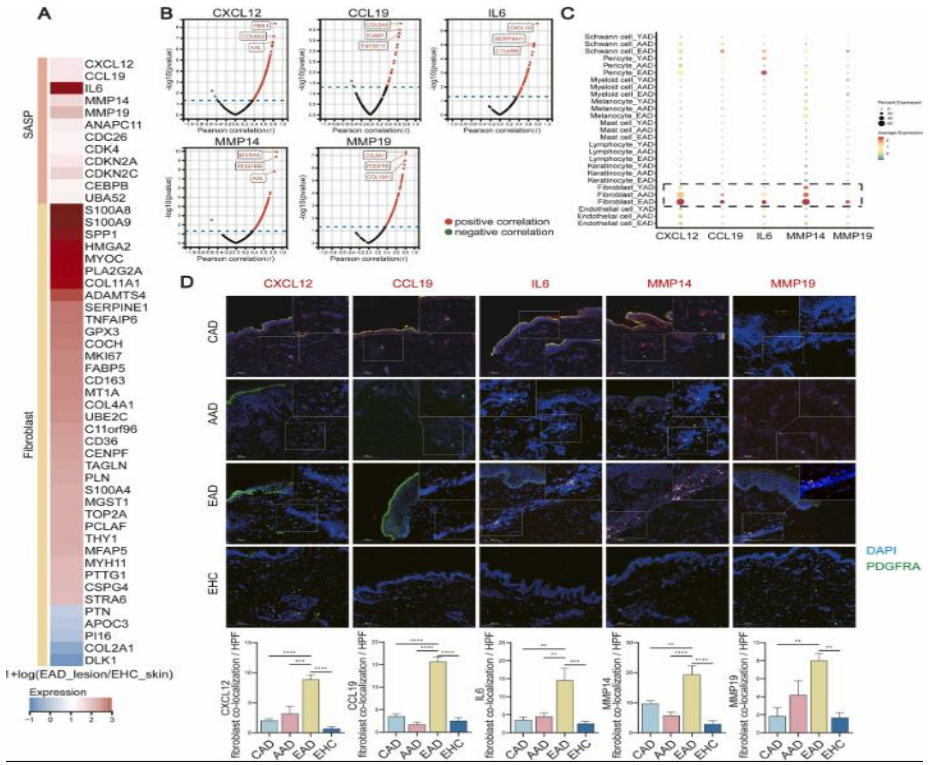


Ionotropic Activity of Kainate Receptors
Diseases of Mitotic Cell Cycle
Zinc Influx into Cells by the SLC39 Gene Family
Cellular Senescence
Free Fatty Acid Receptors
Zinc Transporters
Conversion from APC/C:CDC20 to APC/C:CDH1 in Late Anaphase
Phosphorylation of the APC/C
Senescence-Associated Secretory Phenotype (SASP)
Aberrant Regulation of Mitotic Exit in Cancer Due to RB1 Defects
RNA Degradation
Hypertrophic Cardiomyopathy (HCM)
Pentose Phosphate Pathway
Vascular Smooth Muscle Contraction
Oocyte Meiosis
NOD-Like Receptor Signaling Pathway
Dilated Cardiomyopathy
Ubiquitin-Mediated Proteolysis
Progesterone-Mediated Oocyte Maturation
Alanine, Aspartate and Glutamate Metabolism
Anaphase-Promoting Complex
Zinc Ion Transmembrane Transporter Activity
Beta-2 Adrenergic Receptor Binding
MCRD-Mediated mRNA Stability Complex
Regulation of Phospholipid Translocation
Striated Muscle Cell Development
G Protein-Coupled Opioid Receptor Signaling Pathway
Aging
Acetylcholine Receptor Binding
G Protein-Coupled Opioid Receptor Activity

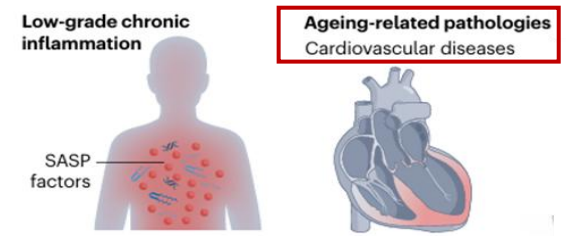


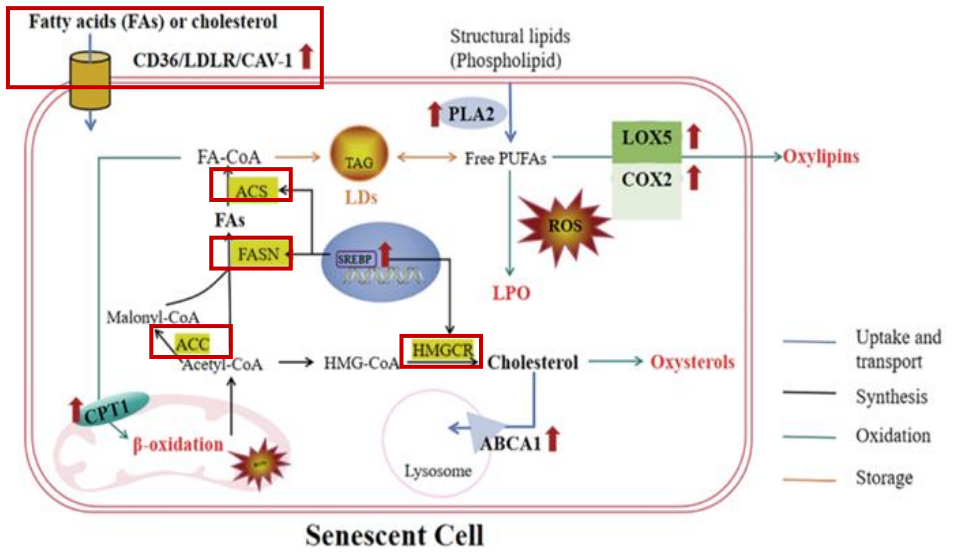
Results 3: Trajectory and clustering analysis

Elderly onset AD have increased SASP levels originated from fibroblast cells.



Chronic, mixed, low-grade inflammation may compromise cardiovascular health.





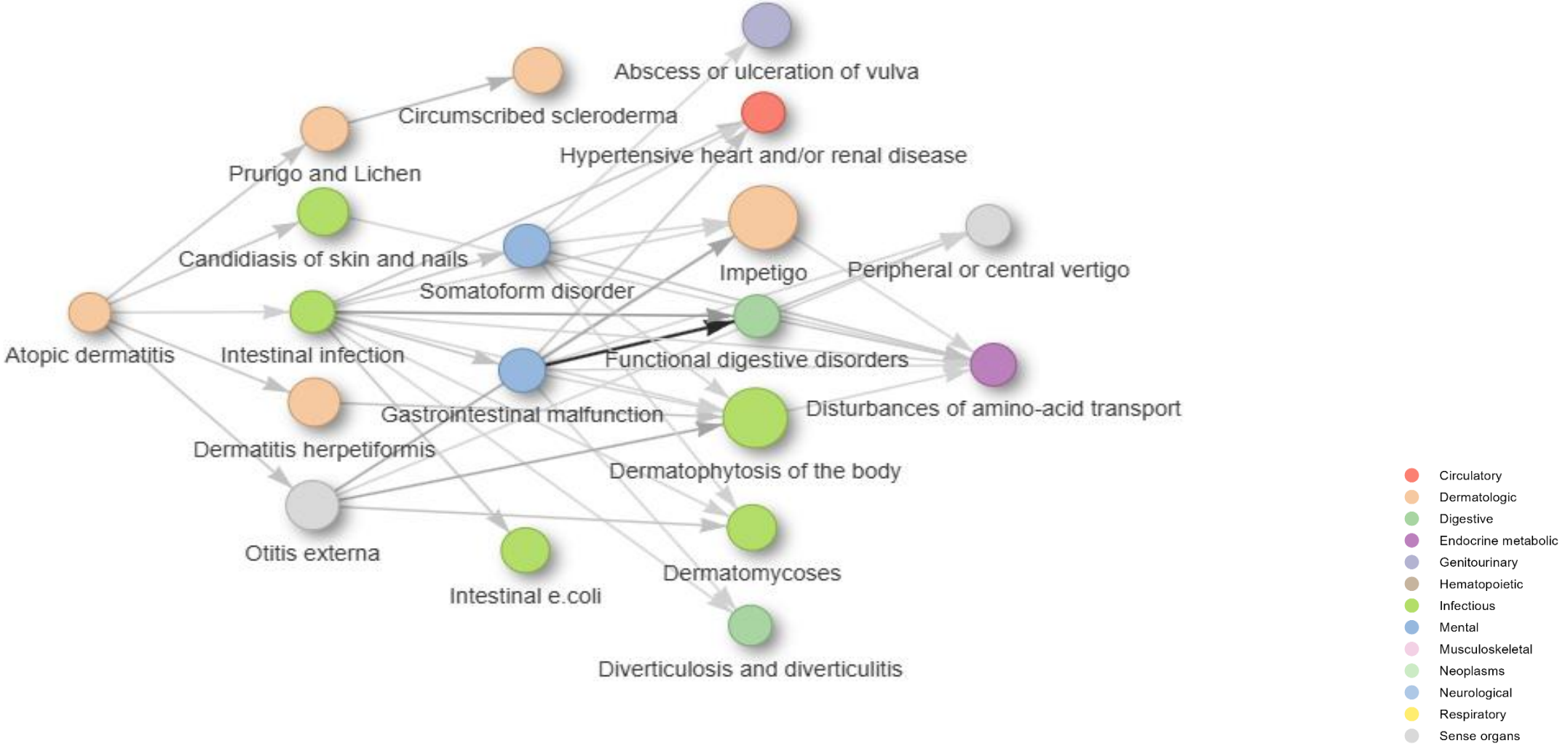
Anti-mixed inflammation and anti-senescence interventions may have multiple benefits for both skin and circulatory system.

J Dermatol Sci. 2024 Jun;114(3):94-103; Nat Rev Mol Cell Biol. 2024 Dec;25(12):958-978; Ageing Res Rev. 2024 Jun;97:102294

Results 3: Trajectory and clustering analysis

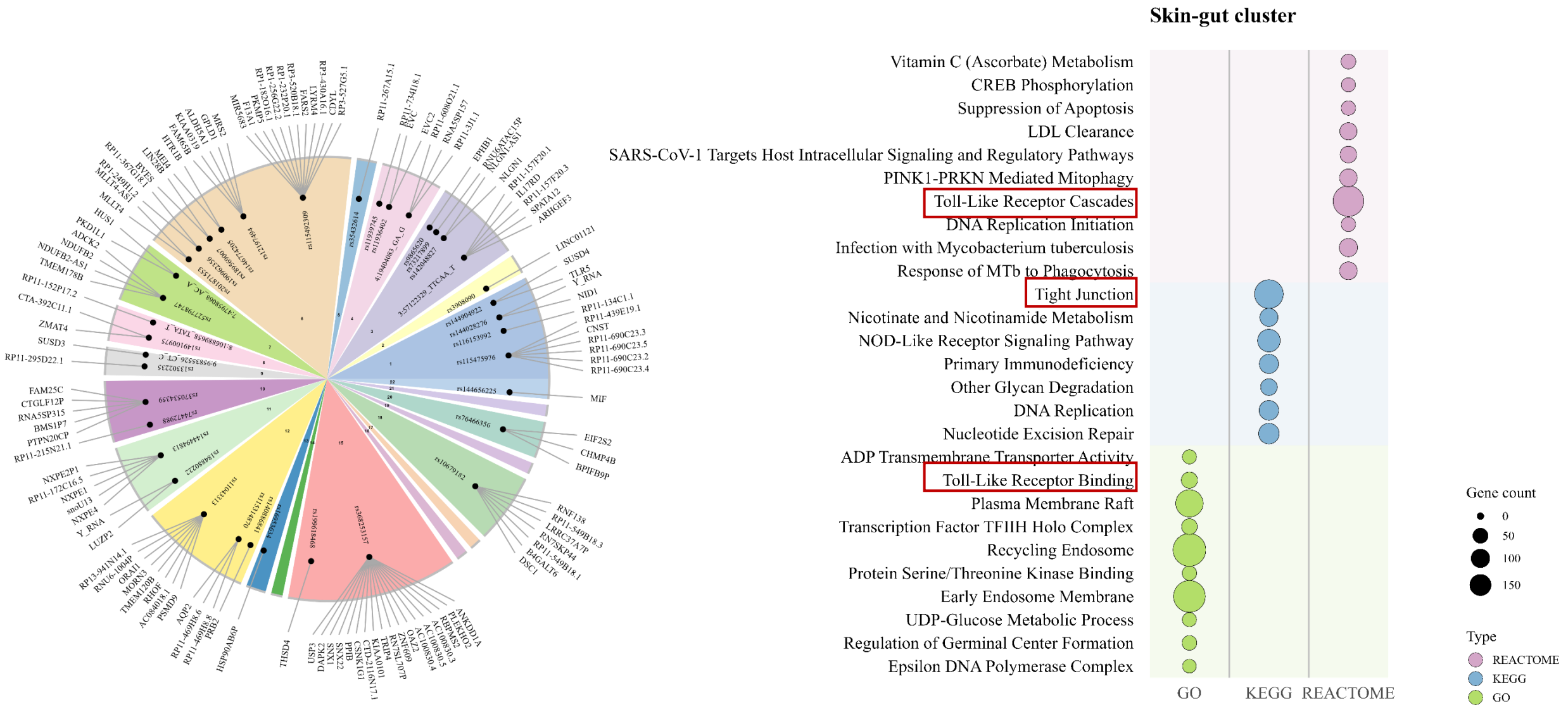
Skin-gut cluster

This cluster consisted of initiated skin and gut infections and subsequent functional digestive disorders.



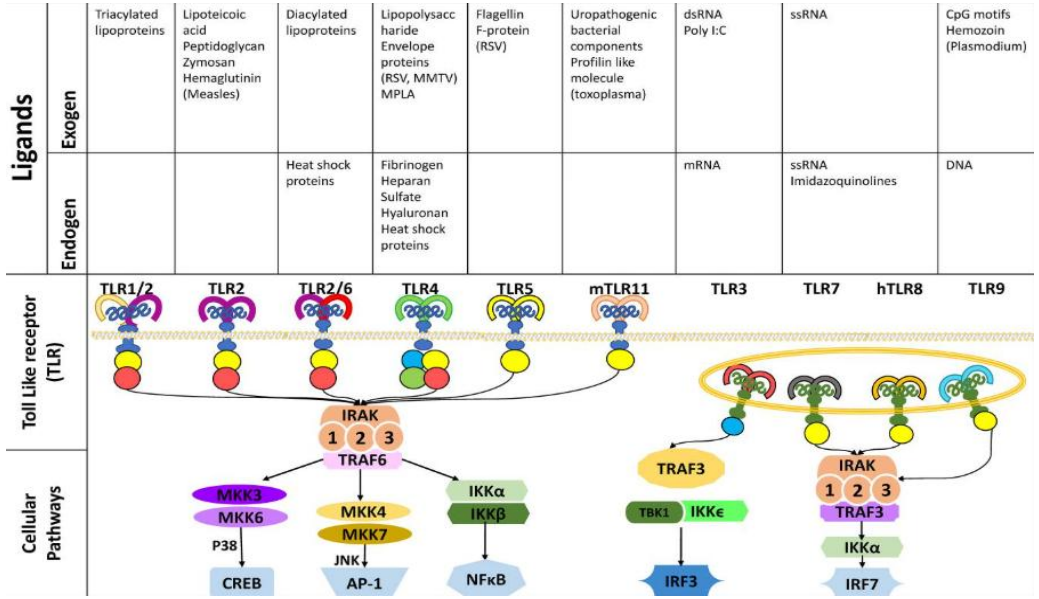
Results 3: Trajectory and clustering analysis

Toll-like receptor and tight junctions were enriched.

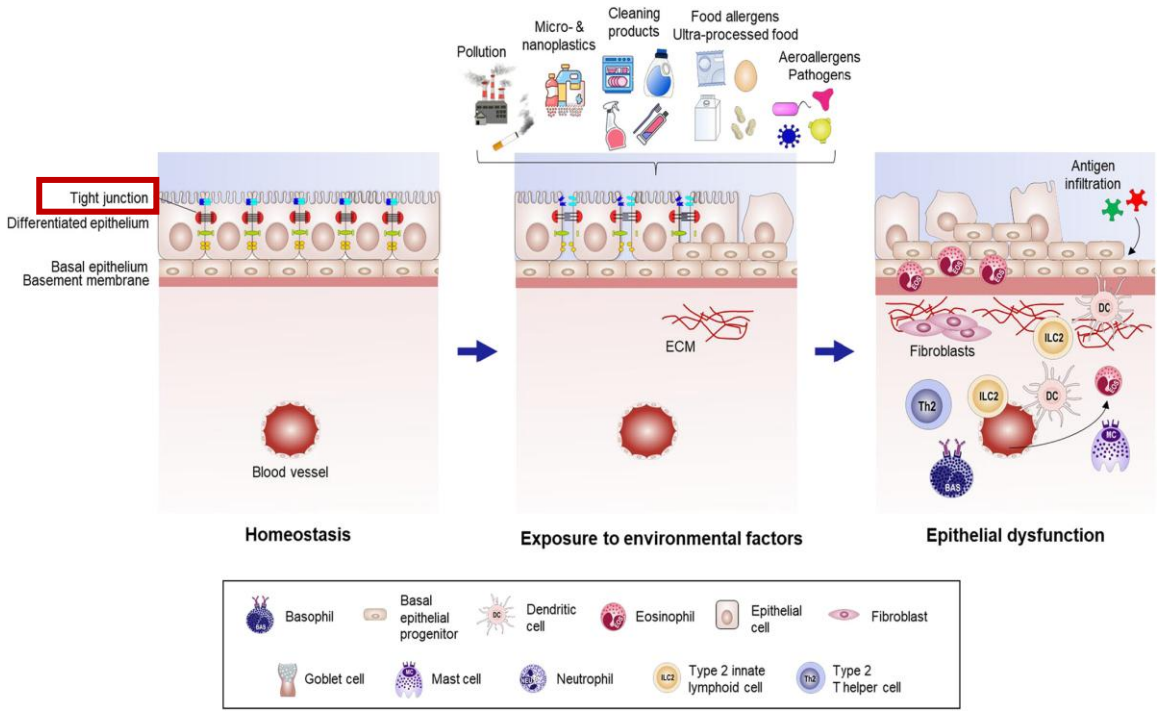


Results 3: Trajectory and clustering analysis

Toll-like receptors (TLRs) are a critical component of host defense against pathogens.



Tight junctions are an integral component of the cutaneous barrier.



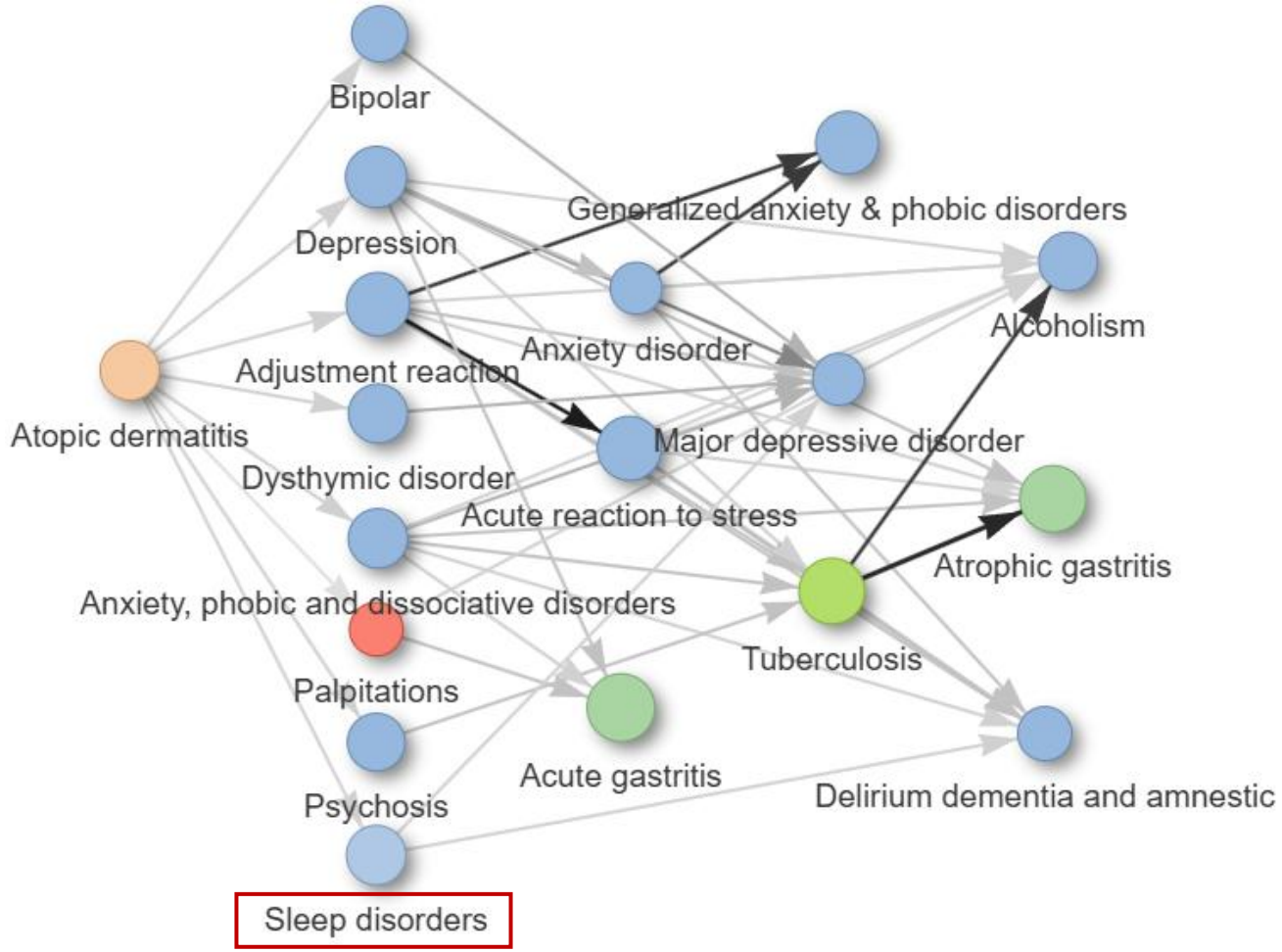
Treatment should focus on enhancing innate immune mechanisms and preserving barrier integrity.

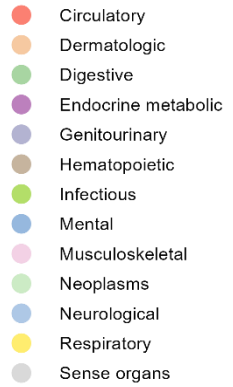
Heliyon. 2025 Jan 31;11(3):e42226; Allergy. 2024 Jun;79(6):1485-1500

Results 3: Trajectory and clustering analysis

Mental cluster

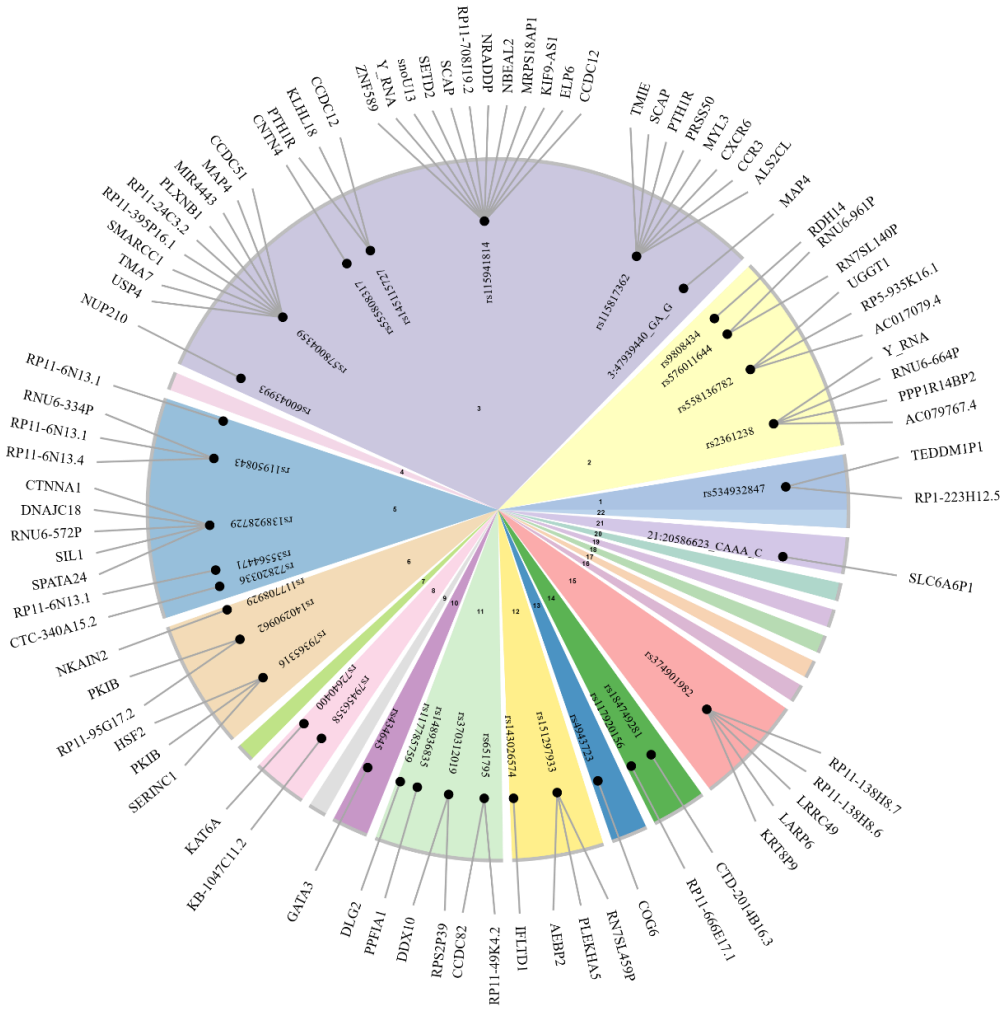
This cluster included initiated sleep disorder, anxiety, depression, progressed to major depressive disorder, and medications-related side effects and ultimately evolved to dementia.

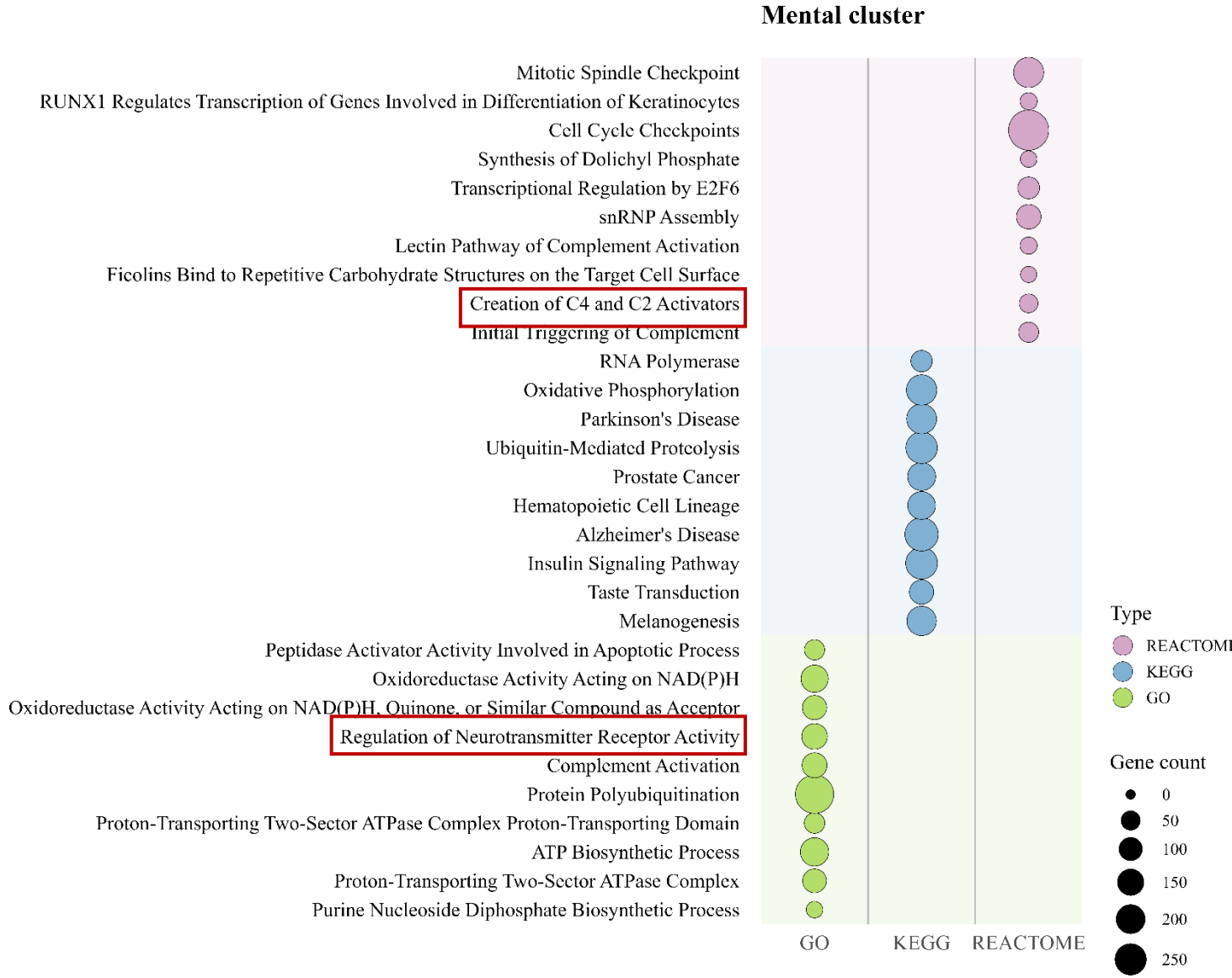




Results 3: Trajectory and clustering analysis

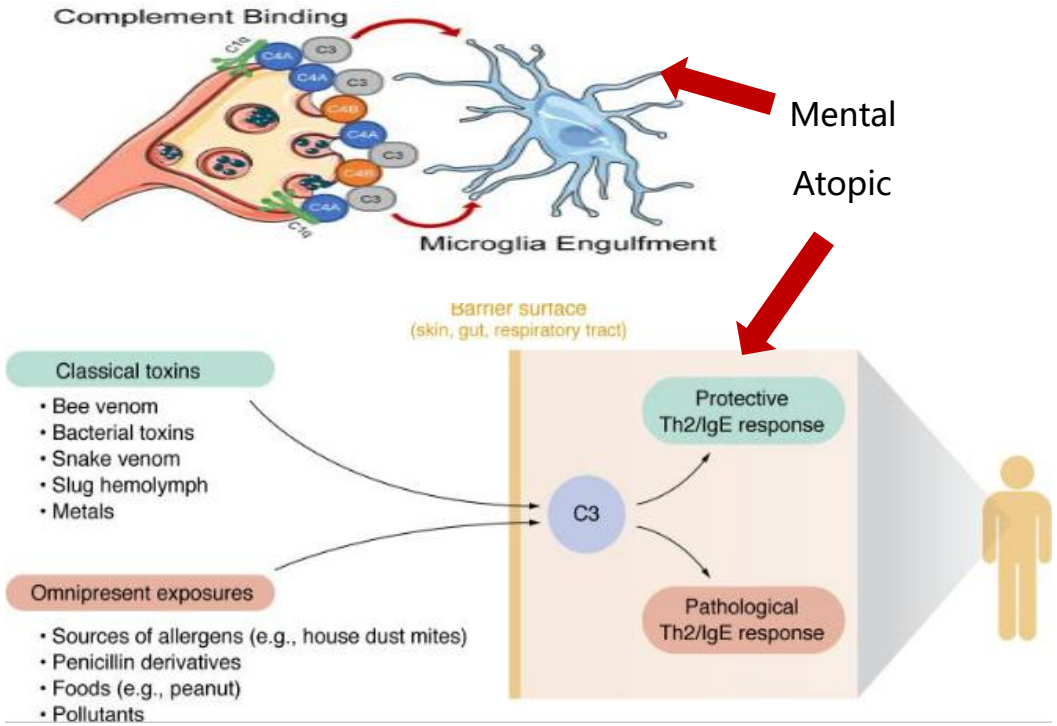
The complement activation and neurotransmitter receptor activity were enriched.



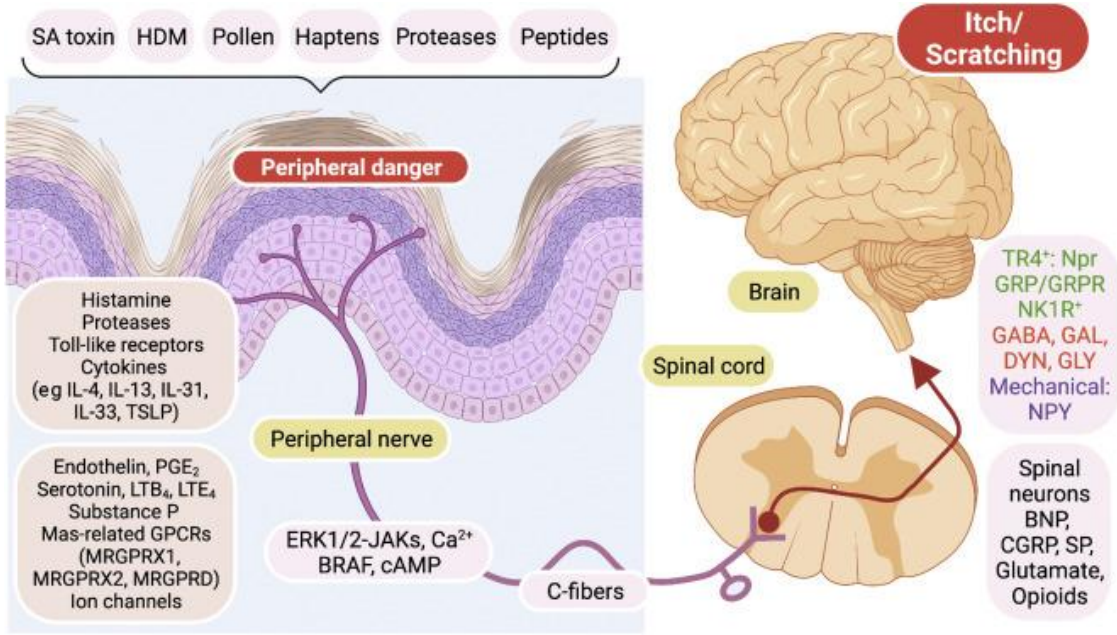


Results 3: Trajectory and clustering analysis

Complement activation is both associated with allergic responses and psychiatric disorders.



Persistent pain and itch in AD may modulate the function of neurotransmitter receptor, thereby contributing to mental comorbidity.



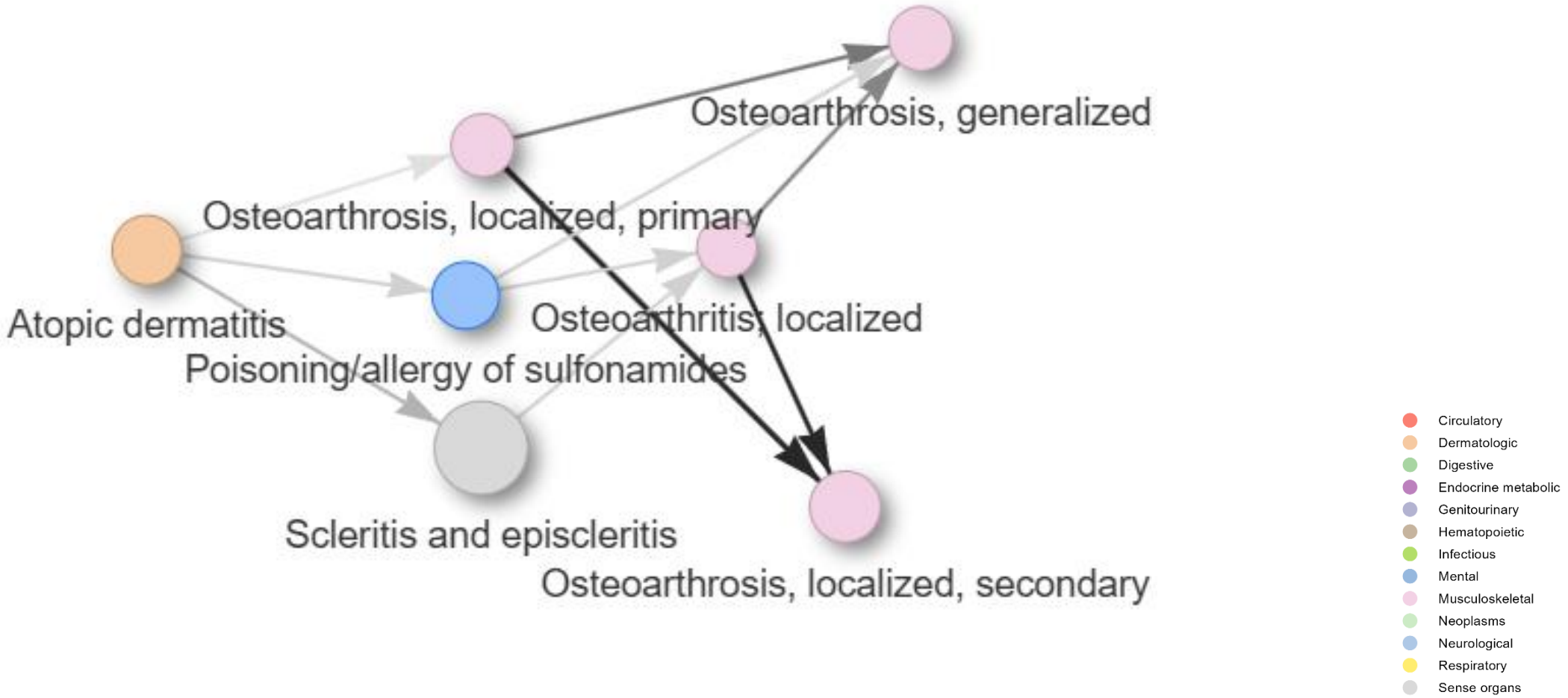
Early screening of mental diseases especially the sleep disorder, and suggest the interventions targeted on inflammation–neural response interactions.

Neurosci. 2021 Feb;24(2):214-224; Mol Neurobiol. 2025 Jul 11 J Clin Invest. 2025 May 1;135(9):e188352; Science. 2025 Jan 31;387(6733):eadn9390; J Allergy Clin Immunol. 2022 Jun;149(6):1875-1898.

Results 3: Trajectory and clustering analysis

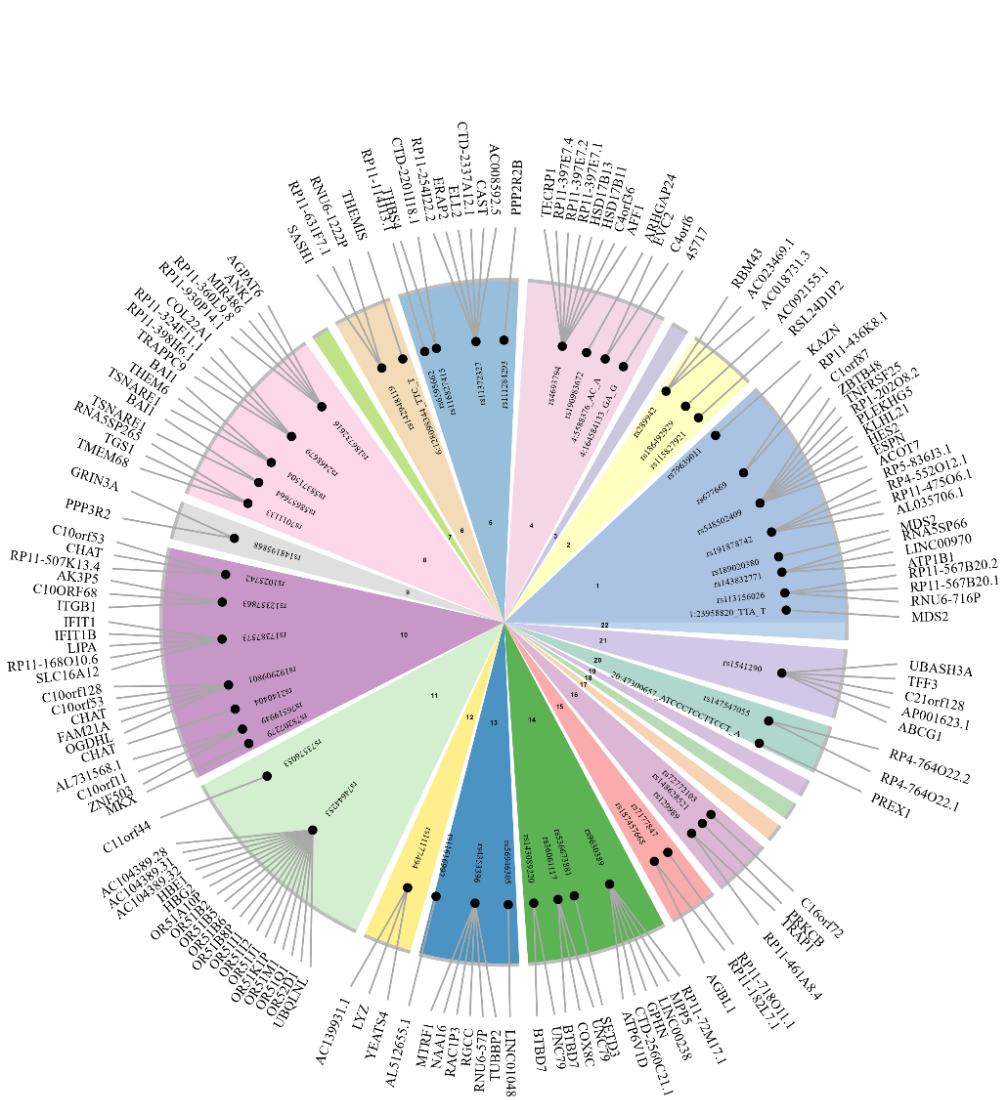
- **Musculoskeletal cluster**

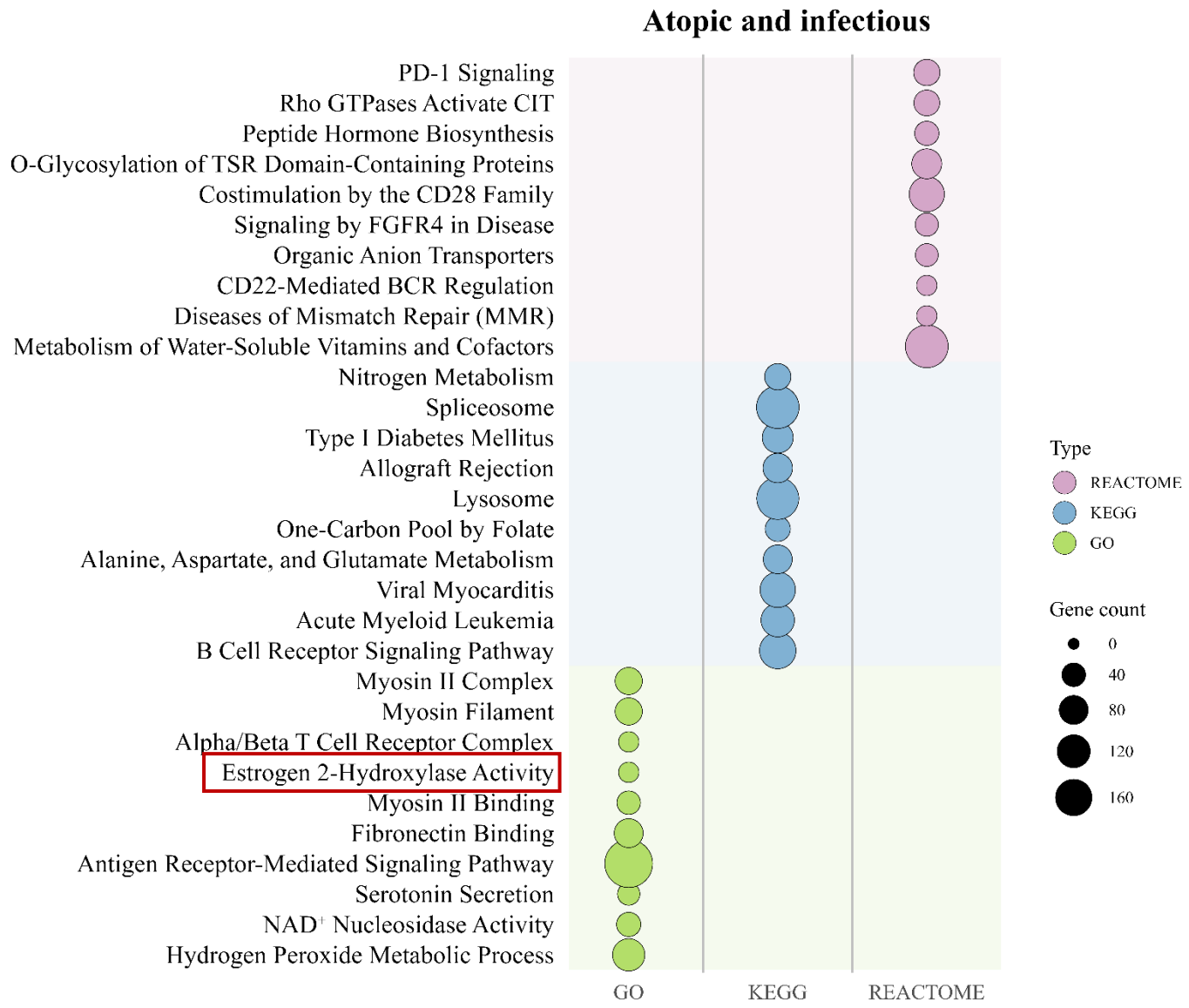
Musculoskeletal cluster demonstrated a trajectory of osteoarthritis progressing from primary and localized stage to generalized and secondary forms.



Results 3: Trajectory and clustering analysis

Estrogen activity was enriched.





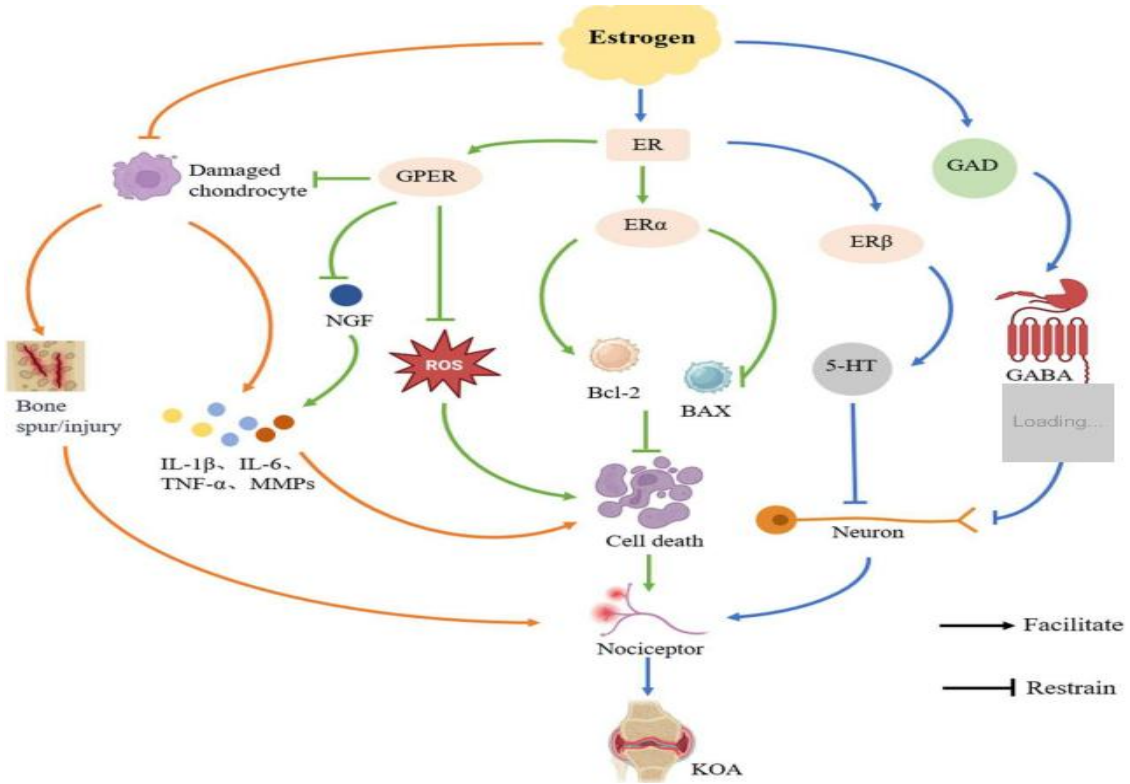
Results 3: Trajectory and clustering analysis

A study reported that women with AD have lower estrogen levels than healthy controls.

Comparison of hormone results during minipuberty between girls with AD and girls in the control group.

	Girls with AD		Control girls		p
	Mean ± SD	Median (Q1–Q3)	Mean ± SD	Median (Q1–Q3)	
Age (weeks)	9 ± 2.3	9 (8–11)	7.7 ± 2.4	7 (6–10)	0.082
Weight (kg)	5.7 ± 0.67	5.6 (5.1–6.4)	4.9 ± 0.66	4.9 (4.5–5.2)	**<0.001**
Length (cm)	57.3 ± 2.7	56 (55–59)	54.1 ± 2.99	54 (52–55)	**0.001**
BMI (kg/m2)	17.4 ± 1.3	17.1 (16.3–18.3)	16.6±1.3	16.6 (15.6–17.4)	0.049
Weight SDS	0.87 ± 0.91	0.68 (0.34–1.57)	0.25 ± 0.95	0.23 (−0.52 to 0.97)	**0.03**
Length SDS	−0.2 ± 0.8	−0.15 (−0.9 to 0.54)	−0.83 ± 1.02	−0.83 (−1.75 to −0.06)	0.024
Weight-for-length SDS	1.12 ± 0.81	1.13 (0.52–1.69)	1.2 ± 0.93	1.28 (0.55–2.09)	0.759
FSH (U/L)	5.43 ± 4.32	3.83 (2.48–7.22)	7.1 ± 7.91	3.74 (2.07–10.4)	0.869*
LH (U/L)	0.34 ± 0.38	0.2 (0.1–0.4)	1.2 ± 2.42	0.4 (0.1–0.9)	0.353*
Estradiol (ng/L)	6.8 ± 4.4	5 (5–6.4)	9.4 ± 5.1	7.9 (5–12.4)	**0.023** *
Testosterone (µg/L)	7.3 ± 9.7	2.5 (2.5–12.7)	10.7 ± 10.1	8.5 (2.5–15.3)	0.056*
Prolactin (µg/L)	35.7 ± 32.1	31 (15–41)	37.4 ± 14.1	32 (26–49)	0.223*
DHEA-S (µg/dL)	41.1 ± 33.1	27 (18–56)	56.2 ± 44.5	39 (26–65)	0.099*
TSH (mU/L)	3.57 ± 2	2.93 (2.2–4.89)	2.3 ± 1.9	1.9 (0.58–4.37)	**0.034**
FT4 (ng/L)	13.8 ± 1.4	13.7 (12.6–15)	16.2 ± 2.4	16.4 (14.5–18.2)	**<0.001**

Estrogen withdrawal has been associated with osteoarthritis



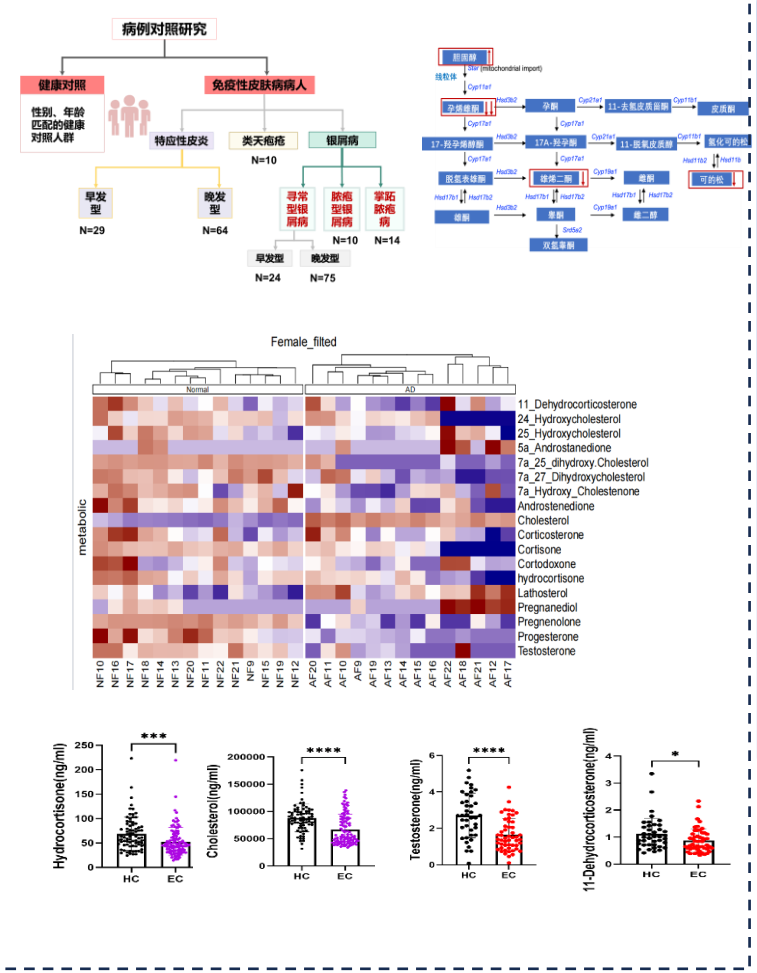
A subset of women with AD may exhibit hormonal dysregulation, for whom hormone-targeted (particularly estrogen-modulating) therapies could be therapeutically relevant.

Turk J Med Sci. 2023 Nov 21;54(1):330-337. J Allergy Clin Immunol Pract. 2022 Aug;10(8):2066-2073; Int J Mol Sci. 2025 Mar 7;26(6):2391.

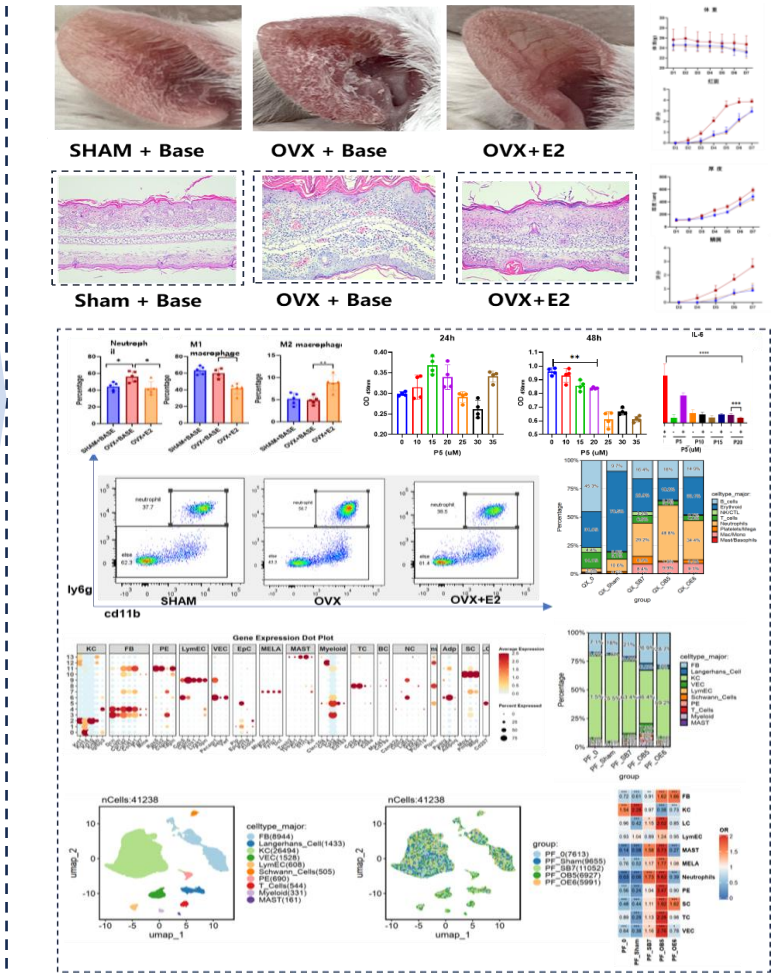
Results 3: Trajectory and clustering analysis

The sex hormone dysregulation in adult-onset female AD

Clinical findings



In vivo study



Patent licensing

国家知识产权局

410000

湖南省长沙市天心区芙蓉南路一段 979 号天城商业广场 8 栋、9 栋 1311 长沙轩荣专利代理有限公司
汪金连(0731-82684117)

发文日：2024年11月12日

申请号或专利号：202411005144.6　　发文序号：202411120032542O

申请人或专利权人：中南大学湘雅医院

发明创造名称：孕烯醇酮作为活性成分在制备银屑病或特应性皮炎的治疗药物中的应用

发明专利申请公布通知书

上述专利申请，经初步审查，符合专利法实施细则第 50 条的规定。根据专利法第 34 条的规定，该申请在 40 卷 4601 期 2024 年 11 月 12 日专利公报上予以公布。

提示：

1.发明专利申请人可以自申请日起 3 年内提交实质审查请求书、缴纳实质审查费，申请人期满未提交实质审查请求书或期满未足额缴纳实质审查费的，该申请被视为撤回。

2.专利费用可以通过网上缴费、银行/邮局汇款、直接向代办处或国家知识产权局专利局缴纳。缴费时应当写明正确的申请号/专利号、费用名称及分项金额，未提供上述信息的视为未办理缴费手续。了解缴费更多详细信息及办理缴费业务，请登录国家知识产权局官方网站。

3.申请人可以访问国家知识产权局政府网站（www.cnipa.gov.cn），在专利检索栏目中查询公布文本。如果申请人需要纸件申请公布单行本的纸件，可向国家知识产权局请求获取。

4.申请文件修改格式要求：

对权利要求修改的应当提交相应的权利要求替换项，涉及权利要求引用关系时，则需要将相应权项一起替换补正。如果申请人需要删除部分权项，申请人应该提交整理后连续编号的部分权利要求书。

对说明书修改的应当提交相应的说明书替换段，不得增加和删除段号，仅只能对有修改部分段进行整段替换。如果要增加内容，则只能增加在某一段中；如果需要删除一个整段内容，应该保留该段号，并在此段号后注明：“此段删除”字样。段号以国家知识产权局回传的或公布/授权公告的说明书段号为准。

对说明书附图修改的应当以图为单位提交相应的替换附图。

对说明书摘要文字部分修改的应当提交相应的替换页。对摘要附图修改的应当重新指定。

同时，申请人应当在补正书或意见陈述书中标明修改涉及的权项、段号、图号。

审查员：自动审查
联系电话：010-62356655

审查部门：初审及流程管理部

210305
2023.03

纸件申请，回函请寄：100088 北京市海淀区蓟门桥西土城路 6 号　国家知识产权局专利局受理处收
电子申请，应当通过专利业务办理系统以电子文件形式提交相关文件。除另有规定外，以纸件等其他形式提交的文件视为未提交。

Take home message

Yinli Zhou, M.D.

- The comorbidity network and its temporal trajectories display divergence and clustering, resolving into five principal clusters with distinct genetic contributors ,which can nominate potential therapeutic targets.
- The concept of AD heterogeneity should be expanded to heterogeneity of **AD syndemics**, thereby informing targeted clinical interventions.

xiaoyixy@csu.edu.cn