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Review article

Comorbidities of atopic dermatitis—what does the evidence say?

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Atopic dermatitis (AD) is a common disease that is associated with atopic and nonatopic comorbidities. There has been a growing interest in this area of AD, because presence or risk of comorbidities can in many ways impact the management of patients with AD. Thus, some treatments for AD may improve its comorbidities as well, whereas others may increase their risk. In this review article, we discuss various comorbidities of AD mostly on the basis of the results of recent multiple systematic reviews and meta-analyses to update readers about this rapidly developing area of dermatology. We emphasize the important information provided by studies presenting both relative risk and absolute risk, and show that AD is associated with, among others, atopic comorbidities such as asthma, rhinitis, and food allergy, nonatopic comorbidities such as ocular, psychiatric, infectious, endocrine, autoimmune, and cardiovascular diseases, and certain cancers. Clinicians need to be aware of these and be cognizant about positive and negative effects of existing and new treatments for AD. (J Allergy Clin Immunol 2023;151:1155-62.)

Key words: *Atopic dermatitis, atopy, asthma, burden, comorbidity, epidemiology*

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Atopic dermatitis (AD) is a common disease affecting about one-fifth of young children at some point and 3% to 5% of adults.[1] Patients with AD typically experience itch, skin pain, and sleep problems, leading to an impaired quality of life.[2] Childhood AD may either persist or resolve by adulthood.[3-7] Onset or recurrence of AD commonly occurs in adulthood.[8-10] Several disease trajectories may occur in children with AD.[11-13] Some of these are associated with higher rates of atopic comorbidities such as food allergy, asthma, and rhinitis (Christensen et al, unpublished data, 2022).[14,15]

There is a growing interest in the comorbidities of AD, which in many ways can impact the management of patients with AD. In some patients, a cross-specialty approach should be encouraged, wherein the overall burden of AD and its atopic and nonatopic comorbidities are diagnosed and treated in the same setting. Old and new treatments for moderate to severe AD may improve not only the signs and symptoms of AD but also comorbid atopic/allergic and autoimmune conditions. Some of these improvements are frequently observed in patients with AD (eg, cyclosporin may improve conjunctivitis and dupilumab may improve asthma), whereas others are infrequently observed (eg, methotrexate and baricitinib may improve RA and baricitinib may improve AA). Comorbid conditions of AD may in turn affect treatment selection. Moreover, adverse risk (in this context, comorbidities) from some newer systemic AD treatments, such as conjunctivitis, viral infections, and cardiovascular disease (CVD), may be particularly increased in patients with more severe disease, either because they are more often treated with these systemics or because they tend to have, for example, more cardiovascular risk factors or suffer from more severe inflammatory diseases of, for example, the eyes.[16] This narrative review article updates the reader on the comorbidities of AD.

Abbreviations used
AA: Alopecia areata
AD: Atopic dermatitis
AR: Absolute risk
CCI: Charlson comorbidity index
CVD: Cardiovascular disease
IBD: Inflammatory bowel disease
JAK: Janus kinase
MOF: Major osteoporotic fracture
RA: Rheumatoid arthritis
SR: Systematic review

Selected association data presented in Fig 1 provide an overview of overall effect sizes from large systematic reviews (SRs) and meta-analyses. Guidelines are beginning to recommend that health care providers address nonatopic comorbidities also in their patients.[17]

METHODOLOGICAL CONSIDERATIONS

When interpreting data from various epidemiological studies as well as SRs and meta-analyses, it is important to acknowledge that inherent limitations exist. The quality of an SR is based on the quality of the included studies ("garbage in–garbage out"); for example, ascertainment bias in the underlying clinical and survey studies of an SR may affect the outcome of the meta-analysis; that is, some members of a target population are more likely than others to be selected in a sample. Moreover, in some studies, severity categorization of patients with AD is based on clinical observation, whereas in other studies, it is based on medication use. Relative risk (RR) estimates show the ratio of a given outcome in the exposed group (patients with AD) in comparison with that in an unexposed group (controls). RR estimates allow for comparison across different studies because these estimates are stable across various populations with different baseline risk estimates. RR estimates are often presented as odds ratios in cross-sectional studies and as hazard ratios in prospective studies and are useful in meta-analyses. As RR estimates cannot discriminate between large and small absolute differences, studies should preferably also present absolute risk (AR) estimates. These are particularly important for clinicians because these can be used to assess how frequently they may come across a given comorbidity in their patients. Although one cannot extrapolate AR estimates in 1 study, combining AR and RR can allow clinicians to calculate the risk in their own patient population. For example, an RR of 2 is calculated not only if an event occurs in 2 of 100 in the case group and 1 of 100 in the control group but also if the event occurs in 200 of 100 in the case group and 100 of 100 in the control group. Therefore, absolute numbers are also needed for proper interpretation of overall risk. An illustrative example of the fundamental difference between AR and RR can be seen in a nicely conducted UK study that showed significantly increased RR of CVD in patients with severe AD.[18] News media reported this novel finding widely, but when analyzing the AR in the UK data set, it was apparent that it was very low, and that clinicians would need to see thousands of patients with AD each year to come across the 1 patient in whom AD was responsible for myocardial infarction.[19] Clinicians should be wary of statistically significant differences between groups in large data sets that have low AR or clinical significance. SRs often do not provide AR estimates, so it is often possible to get such data only from looking into individual studies. In this article, we therefore refer to low AR from specific articles, but acknowledge that AR is dependent on AD severity of the source population as well as age, ethnicity, and many other factors.

Efforts were recently made to identify the best search terms algorithms for AD research using SRs, because this may profoundly impact the number of articles retrieved and hence the outcome of a meta-analysis.[20] The number of languages used during the screening, the number of databases included, as well as their origin are key to ensure broad inclusion of studies from all around the world. The diagnostic criteria for AD are important because these may dramatically impact risk estimates (as in a Danish survey on CVD risk).[21] When possible, stratification for clinical characteristics, most notably, disease severity, disease activity, and lifestyle factors, should be done because these will impact the risk of having or developing comorbidities.

Atopic comorbidities

Recent comprehensive SRs and meta-analyses informed in detail about the overlap between AD and atopic conditions. In individuals with AD, the overall pooled prevalence of rhinitis, asthma, or both is 40.5%, 25.7%, and 14.2%, respectively.[22,23] In adults with AD, 28.6% and 24.1% have food sensitivity and food allergy, and even higher proportions were observed in children with AD (Christensen et al, unpublished data, 2022). Food challenge–proven food allergy is also common in children and adults; egg was found to be the most common allergen. Patients with AD have 3- to 4-fold increased odds of having an atopic disease (Christensen et al, unpublished data, 2022),[22,23] which in part is explained by shared genetics.[24] Furthermore, more severe AD is associated with increased likelihood of atopic comorbidities, including asthma (Christensen et al, unpublished data, 2022).[22,23,25] Importantly, AD is associated with both allergic and nonallergic forms of asthma and rhinitis defined from specific IgE measurements and skin prick tests.[22,23] Little is currently known about the overlap between AD and other conditions characterized by type 2 inflammation, such as nasal polyposis and eosinophilic esophagitis. These disorders are less common overall, but are more common in patients with AD.[26,27] Clinicians should consider screening their patients with AD for gastrointestinal and respiratory atopic symptoms because this may impact treatment selection.

Ocular comorbidities

Anterior subcapsular cataract, keratoconus, and recurrent conjunctivitis are minor Hanifin and Rajka criteria for AD, emphasizing that ocular disease is a part of the AD syndrome.[28] The high prevalence of ocular adverse events, including conjunctivitis and blepharitis, secondary to inhibitors of IL-13 and IL-4 signaling in patients with AD, led to renewed interest in ocular comorbidity of AD.[29] An SR showed that the prevalence of conjunctivitis was 31.7% in patients with AD and 13.3% in controls, the most common subtypes in patients with AD being allergic conjunctivitis, whereas atopic keratoconjunctivitis and infectious conjunctivitis were much less common.[30] Blepharitis affected 22.0%, dry eye disease 9.1%, and keratitis 1.4%, whereas keratoconus affected less than 1%. Clinicians

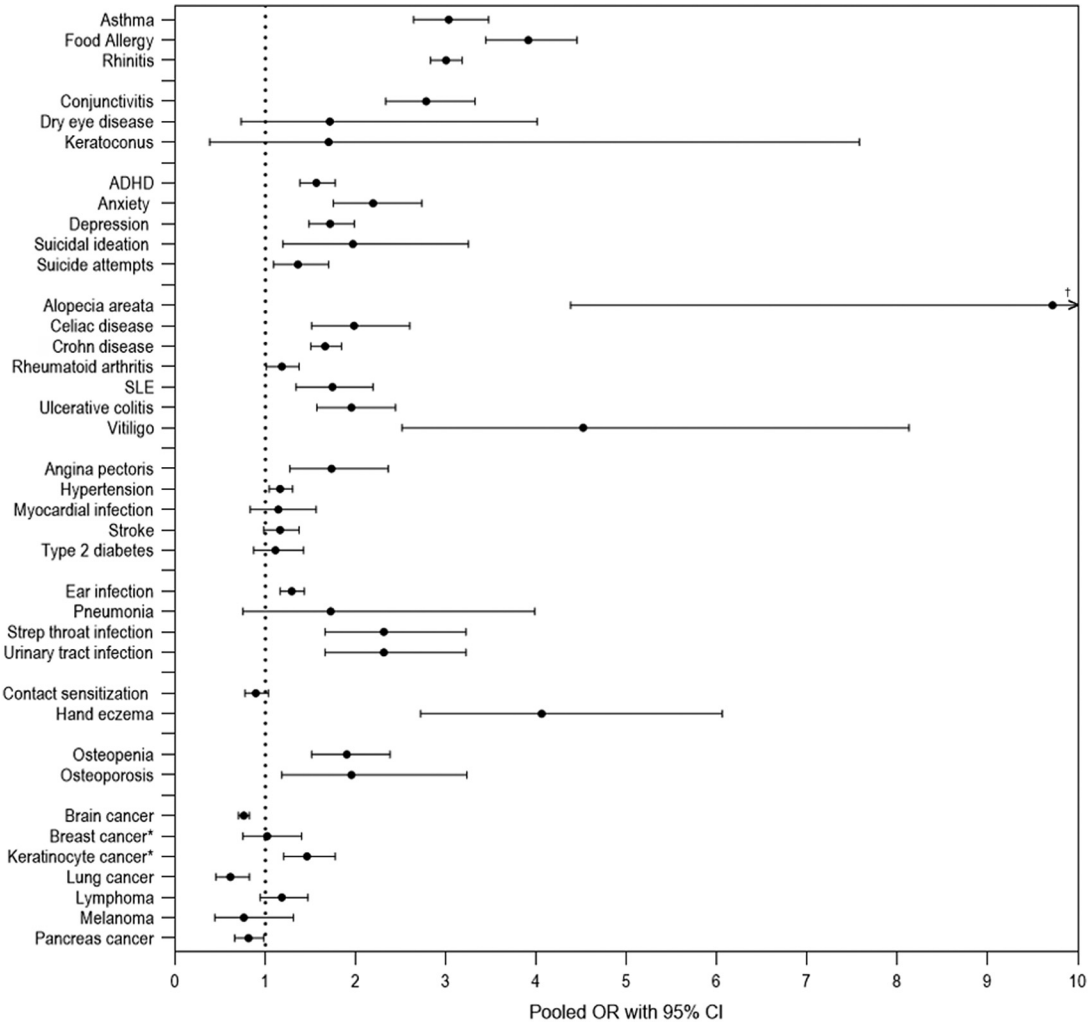

FIG 1. Forest plot of pooled ORs with 95% CIs for the risk of comorbidities in patients with AD derived from recent SRs and meta-analyses. Pooled ORs with 95% CIs were extracted from the following references: asthma[22]; food allergy (Christensen et al, unpublished data, 2022); rhinitis[23]; conjunctivitis, dry eye disease, and keratoconus[30]; ADHD[35]; anxiety[32]; depression and suicidal ideation[31]; suicide attempts[33]; alopecia areata, celiac disease, Crohn disease, rheumatoid arthritis, SLE, ulcerative colitis, and vitiligo[47]; angina pectoris, myocardial infection, stroke, and type 2 diabetes[70]; hypertension[67]; ear infection, pneumonia, strep throat infection, and urinary tract infection[84]; contact sensitization[87]; hand eczema[86]; osteopenia and osteoporosis[100]; brain cancer, breast cancer, keratinocyte cancer, lung cancer, melanoma, and pancreas cancer[103]; and lymphoma.[110] *ADHD*, Attention deficit/hyperactivity disorder; *OR*, odds ratio; *SLE*, systemic lupus erythematosus. *Standardized incidence ratios are presented instead of ORs. †95% CI, 4.38-21.59.

should ask about ocular symptoms and perform clinical examinations when relevant to reduce the burden of comorbid ocular disease. Some ocular comorbidities may indirectly worsen underlying AD, such as eye pruritus from allergic conjunctivitis leading to chronic rubbing around the eyes and secondary eczematization.

Psychiatric comorbidities

The impact of AD on mental health can be substantial. The AR of psychiatric comorbidity is high in both pediatric and adult patients with AD[31] and should be considered by clinicians in clinical practice.

Among all the SRs and meta-analyses, there were 2 that examined the relationship of AD with depression, suicidality, and/or anxiety.[31,32] The first included 23, 13, and 6 studies in the meta-analyses of depression, anxiety, and suicidality, respectively, and found significantly higher odds of AD with depression and anxiety in adults, depression in children, and suicidality in adults and adolescents.[32] Risk of depression and anxiety was increased 2-fold, and risk of suicidal ideation 4-fold.[32] The second included 36 studies with sufficient data for meta-analysis and found that 20.1% (1 in 5 persons) with AD had depression compared with only 14.8% of controls.[31] Adult patients with AD had significantly higher rates of clinical depression (14.9% vs 12.6%), numerically higher rates of antidepressant use (29.3% vs 20.3%), and significantly higher rates of suicidality (12.2% vs 6.4%).[31] Depression occurred particularly in patients with moderate to severe AD.[31] Depression and antidepressant use particularly occurred in adults.[31] Children with AD also had

higher prevalence of parental depression compared with children without AD (29.3% vs 20.3%).[31] Two SRs showed that suicidal ideation risk was increased 1.5 times and suicidal attempt was also significantly increased.[33,34] An SR specifically in children confirmed the association between AD and psychiatric disease.[35] It is currently unclear whether AD has a causative genetic effect on depression.[36-38] AD was also associated with attention deficit/hyperactivity disorder and with its severity.[35,39,40] Four studies in the aforementioned SR[31] found that different topical, oral systemic, or biologic treatment regimens for AD improved depression and/or depressive symptoms.[41-44] These studies suggest that depressive symptoms occurring in AD may be directly related to AD severity and modifiable with reduced AD severity. A Danish registry study showed that the risk of being hospitalized for clinical depression or anxiety is similar to that of the general population.[45] Recent AD guidelines from the American Academy of Dermatology recognize that AD in adults is associated with clinician-diagnosed depression and anxiety (moderate-quality evidence) and may be associated with suicide (low-quality evidence).[17]

Autoimmune comorbidities

The odds ratio of alopecia areata (AA) in patients with AD is increased up to 10-fold, and similar to atopic comorbidities, the association is bidirectional.[46,47] AA may be more severe in the context of AD and in the presence of filaggrin gene mutations.[48] Large studies showed increased risk of developing AA in patients with atopic conditions, with the risk increasing with each additional atopic condition.[49,50] IL-13 has also been shown to be the strongest genetic association in a large genome-wide association study in patients with AA and atopy as well as in patients with AA alone.[51] Other autoimmune diseases, particularly vitiligo, but also chronic urticaria, celiac disease, inflammatory bowel disease (IBD), systemic lupus erythematosus, and rheumatoid arthritis (RA), are also more common in patients with AD compared with controls, typically 1.5- to 2-fold, in part explained by shared genetic risk variants.[40,47,52-58] On the basis of the data from a Danish registry study, the risk of autoimmune disease is elevated in patients with AD who have a smoking history.[55] A US population–based survey study found higher odds of self-reported RA and systemic lupus erythematosus in adults with AD, particularly those with atopic comorbidities.[59] A large-scale US inpatient study found the prevalence of autoimmune disease to be higher in adults (7.9% vs 5.7%) and children (2.0% vs 1.0%) with and without AD.[60] AD was associated with 18 of 32 autoimmune disorders examined in adults and 13 of 24 examined in children, including AA, vitiligo, Hashimoto disease, and IBD.[17] The association between type 1 diabetes and AD remains unclear, but the evidence indicates that the risk is reduced in AD.[61]

Cardiovascular risk factors and comorbidities

It is a subject of much debate whether patients with AD have increased risk of CVD similar to patients with psoriasis, and whether this is explained by systemic inflammation or lifestyle factors.[28,62,63] SRs studying lifestyle factors showed that AD is associated with smoking[64] and being overweight and obese in Asian and North American populations but not in a European population,[65] but AD is not associated with alcohol use.[66] An SR on the association between AD and hypertension showed a positive association, especially in patients with severe disease.[67] It further showed that cyclosporin use increased this risk. The association between AD and type 2 diabetes is, so far, scarcely studied, but it is possible that an elevated risk, at least in part, can be explained by prolonged and intense use of topical corticosteroids.[68] Three meta-analyses recently examined the associations of AD with CVD.[69-71] They showed very modestly elevated risk for various outcomes and that residual confounding may be a risk.[17] However, on the basis of experimental studies showing elevated CVD biomarkers in patients with moderate to severe AD,[72,73] and a large UK registry study showing increased CVD risk in patients with severe AD,[18] the current understanding is that inflammation in AD may alter the risk in itself but that the AR is small. Given that CVD is common in many ethnicities across the world, dermatologists may diagnose and address CVD risk factors in their patients when relevant. A recent SR showed that the risk of incident venous thromboembolism was not increased in patients with AD compared with controls.[74]

Infectious comorbidities

AD leads to impaired cellular immunity, and the risk of viral skin infection is therefore increased. Accordingly, AD is associated with herpes simplex, varicella zoster, verrucae, and molluscum contagiosum.[75] Some studies show that the risk of infections from coronavirus disease 2019 is also slightly increased in patients with AD, whereas other studies show similar risk.[76-80] Patients with AD have a 20-fold increased risk of being colonized with *Staphylococcus aureus* and with a severity-dependent association.[81] Methicillin-resistant Staphylococcal infection is also associated with AD.[82] These observations translate into an increased occurrence of skin infections such as erysipelas and impetigo, but in rare cases this may also lead to bone infections, sepsis, encephalitis, and endocarditis in patients with AD.[75,82,83] An SR showed 1.3- to 2-fold increased risk of ear infection, strep throat, and urinary tract infection in patients with AD.[84] In separate studies, an increased risk of upper and lower respiratory tract infection was also associated with both pediatric and adult patients with AD.[83,85] One US study showed 1.5-fold increased risk of tuberculosis in patients with AD.[82]

Contact dermatitis and hand eczema

AD is associated with hand eczema, because AD may be located on the hands and also because the risk of allergic and irritant contact dermatitis is altered. An SR showed that the point prevalence and lifetime prevalence of hand eczema were increased, respectively 2- and 4-fold, and also that the risk of occupational hand eczema was similarly elevated.[86] An SR on the association with allergic contact dermatitis showed that in patients with milder forms of AD, that is, patients from general population studies, the risk of allergic contact dermatitis was increased 1.5-fold, whereas the risk was significantly decreased in clinical populations including patients typically seen in hospital systems and who therefore had more severe disease.[87] This observation is supported by experimental studies showing how T_H2 deviation and active severe AD reduce the ability to develop contact sensitization.[88] There was no SR conducted on the association between AD and irritant contact dermatitis, and so the relationship remains unresolved, with some studies showing

increased skin reactivity and others similar reactivity as controls.[89-92] However, there is solid evidence that penetration of chemicals, including skin irritants, is increased in AD skin.[93]

Osteoporosis

Various risk factors for osteoporosis are associated with AD, for example, tobacco smoking, physical inactivity, vitamin D deficiency, and use of corticosteroids or psycholeptics, making it plausible that patients with AD are indirectly at increased risk of osteoporosis and major osteoporotic fractures (MOFs).[64,94] The strongest risk estimates were observed in older patients, individuals with severe disease, and users of systemic corticosteroids.[95-97] Systemic inflammation in AD was also proposed as a risk factor for major comorbidities, similar to, for example, Crohn disease.[98,99] Currently, few studies examined the risk of osteoporosis and MOFs, but an SR showed slightly increased risk of MOF and a 2-fold increased risk of osteoporosis and osteopenia.[100] Another SR also found increased risk of MOF and in a severity-dependent manner, but also concluded that differences between studies precluded quantitative analysis.[101] The contribution of topical corticosteroid therapy to the increased risk of bone disease in patients with AD is currently unresolved.[102] Recent AD guidelines from the American Academy of Dermatology recognize that AD in adults is associated with osteoporosis (high-quality evidence) and bone fractures (moderate-quality evidence).[17]

Cancers

There is ongoing interest in the possible association between AD and certain cancers, given concerns about chronic inflammation and possibly anti-inflammatory treatments increasing cancer risk. SRs showed that the risk of keratinocyte cancer is increased about 1.3- to 1.5-fold in patients with AD, whereas the risk of central nervous system and pancreatic cancers is paradoxically decreased.[103,104] In another SR, no association between AD and pancreatic cancer was observed.[105] Risk of skin cancer may be elevated because of lower levels of filaggrin and the degradation product urocanic acid, an important photoreceptor.[106] Danish studies showed not only an elevated risk of actinic keratosis and keratinocyte cancers in patients with AD, but also that individuals with homozygous filaggrin gene mutations (both with and without AD) had a higher risk.[106-109] However, use of phototherapy and cyclosporin may also be an important explanation for the association. An SR showed a slightly increased risk of lymphoma in patients with AD who were part of prospective and retrospective cohort studies, but not in patients from case-control studies.[110] A very small part of the increased risk may be explained by use of topical calcineurin inhibitors in patients with AD.[111,112] Risk studies on cancer in patients with AD may particularly be susceptible to surveillance bias, that is, the fact that patients with AD cared for by dermatologists are more likely to become diagnosed with skin malignancies than individuals who are not seen by dermatologists.

MULTIMORBIDITY AND MORTALITY

The Charlson comorbidity index (CCI) is a weighted index that predicts the risk of death within 1 year of hospitalization for patients with specific comorbid conditions.[113] In Danish adult patients with AD, the CCI score was higher than for controls, but only in patients with AD who smoked.[114] In the United States, the CCI score for adult patients with psoriasis was similar to that for adult patients with AD.[75] In pediatric and adolescent patients with AD, the CCI score was significantly higher than that for controls.[115] The appropriateness of CCI in AD research is debatable, especially in children, but overall CCI has a high validity when using diseases coded in the *International Classification of Diseases, Tenth Revision*.[113] The Healthcare Cost and Utilization Project chronic comorbidity indicator is a modified score that is more appropriate for pediatric research. This score was also significantly increased in US children and adolescents with AD.[115] Few studies examined mortality in patients with AD. Studies from Denmark showed that all-cause mortality was slightly increased compared with controls and that CVD, infections, and urogenital diseases explained the elevated risk.[116] A UK registry study also showed increased all-cause mortality risk and found a severity-dependent association. Infectious, digestive, and genitourinary diseases mainly explained the elevated risk.[117]

IMPACT OF COMORBIDITY ON TREATMENT SELECTION

We have shown how the risk of various comorbidities is increased in patients with AD. Some of these may even be treated with the use of new and old systemic treatments. Although it is beyond the scope of this review article to address this, it is important that clinicians are aware of therapeutic indications of especially newer treatments including Janus kinase (JAK) inhibitors and biologics that are approved for IBD, RA, AA, and severe asthma, and therefore in selected patients with comorbid autoimmune disease, these may be preferred.

Although the long-term safety profile of JAK-inhibitor use in AD is unknown, clinical trial data suggest that the risk of CVD, venous thromboembolism, and cancer is not increased.[118] However, JAK-inhibitor use in general has been associated with an increased risk of cancers and CVD,[119] and therefore, clinicians should prioritize other treatments first in patients with risk factors for developing such serious adverse events. Similarly, a history of conjunctivitis and severe AD is associated with slightly increased risk of ocular surface disease in dupilumab- and tralokinumab-treated patients with AD.[120,121] It is unclear whether the increased occurrence of T_H17-driven diseases such as seronegative arthritis and enthesitis following dupilumab treatment will also be observed with other new treatments.[122]

CONCLUSIONS

In recent years, much evidence of associations between AD and a wide array of comorbidities has emerged. Despite their inherent limitations, recent studies have led to substantial improvement in our understanding of the risk of AD comorbidities.

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