Environmental Risks for Inflammatory Myopathies

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INTRODUCTION

Inflammatory myopathies are a group of heterogenous diseases. Some rare conditions in this group are associated with infections but the larger group, idiopathic inflammatory myopathies (IIMs), the focus of this review, does not have a causative agent. IIM is characterized by proximal muscle weakness accompanied by various extramuscular

KEYWORDS

- Idiopathic inflammatory myopathies
- Myositis
- Antisynthetase syndrome
- Environmental factors
- Ultraviolet radiation
- Smoking
- Infectious agents
- Pollutants

KEY POINTS

- It has been suggested that the onset of idiopathic inflammatory myopathies (IIMs) requires environmental triggers besides underlying genetic susceptibility. Ultraviolet radiation, smoking, infectious agents, certain pollutants, medications, and vitamin D deficiency are potential environmental triggers for IIM.
- Many of the suggested environmental factors for IIM enter human body via lungs and are related to features of lung involvement in IIM, supporting lung as the initial onset site of autoimmunity for some subgroups of IIM.
- Some presented environmental factors are linked to specific IIM phenotypes and the presence of specific autoantibodies, such as anti-Mi2, anti-Jo1, and anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase autoantibodies, indicating the relevance of different environmental factors in different autoantibody-defined subgroups of IIM.
- Future investigations should consider exploring the associations between environmental factors and subsets of IIM defined by autoantibody profile.

INTRODUCTION

Inflammatory myopathies are a group of heterogenous diseases. Some rare conditions in this group are associated with infections but the larger group, idiopathic inflammatory myopathies (IIMs), the focus of this review, does not have a causative agent. IIM is characterized by proximal muscle weakness accompanied by various extramuscular...
manifestations, for example, in skin, lungs, joints, heart, and gastrointestinal tract.\textsuperscript{1,2} The major subtypes of IIM classified based on clinical, serologic, and histologic features are dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), antisynthetase syndrome (ASSD), immune-mediated necrotizing myopathy (IMNM), and juvenile IIM.\textsuperscript{1} More homogenous subsets can be identified by using myositis-specific and myositis-associated autoantibodies (MSAs and MAAs).\textsuperscript{1}

The pathogenic mechanisms of IIM are complex and not fully understood but it has been suggested that the onset of IIM requires environmental triggers in genetically susceptible individuals.\textsuperscript{3} The geospatial and seasonal pattern of IIM onset as well as exposure to different environmental factors before the diagnosis of IIM have been studied and findings suggest associations between various environmental factors and IIM\textsuperscript{4–8} but only a few of them have been reproduced in large-scale studies with comparison to the general population.\textsuperscript{9–12} In this review, we systemically review and discuss the external environmental factors with suggestive evidence mainly from cross-sectional, case-control, and cohort studies for adult-onset IIM (Table 1). We also highlight their potential implications in IIM development, identify current challenges, and provide insight into future investigation.

**Ultraviolet Radiation**

Ultraviolet (UV) radiation has long been considered a risk factor for IIM, in particular for DM. The supportive evidence include (1) photosensitivity being a common cutaneous manifestation associated with DM\textsuperscript{2}, (2) prevalence of DM showing a geographic gradient negatively correlated with latitude\textsuperscript{13,14}, and (3) prevalence of DM positively associated with UV radiation intensity.\textsuperscript{15,16} The association between UV radiation and the development of DM is further supported by evidence from the study using MYOVISION registry data. Based on the self-reported data on sun exposure in 1,350 patients, patients with DM were more likely to experience 2 times or more of sunburn and high/moderate job-related sun exposure 12 months before disease diagnosis than patients with PM or IBM.\textsuperscript{17} Moreover, sun exposure may not only confer the risk of DM development but also DM flare.\textsuperscript{5}

The association between UV radiation and presence of some MSAs/MAAs has been examined, and a positive correlation between the prevalence of DM-specific anti-Mi2 autoantibodies and UV radiation has been suggested.\textsuperscript{15,16} A systematic review analyzing prevalence data from 92 studies across 22 countries showed a significant trend of increasing prevalence of anti-Mi2 autoantibodies with lower latitudes, whereas the trend to increase in higher global solar UV index (UVI) was not significant.\textsuperscript{4} Because UVI was estimated based on data in 2010 while data collection of the included studies spread over a much wider time period (up to 10 years), and because UV radiation was correlated with latitude, it was suggested that analyses of geographic gradient might provide more precise findings than UVI.\textsuperscript{4} Interestingly, the review study also first reported positive associations with UVI for anti-Ro52, anti-PM-Scl, and anti-Ku autoantibodies and a negative association for anti-threonyl-tRNA synthetase autoantibodies,\textsuperscript{4} suggesting that UV radiation may affect the development of other IIM phenotypes besides DM. Further investigation of these associations is warranted given the limitations, such as cross-sectional design and lack of measurement of personal exposure to UV radiation, of the included studies.\textsuperscript{4,15,16}

It has also been suggested that associations between UV radiation and DM and anti-Mi2 autoantibodies differ across sex and ethnicity. The risk of having DM and anti-Mi2 autoantibodies associated with UV radiation and sunburn was solely significant in women, whereas the association between occupational sun exposure and DM was more apparent in men.\textsuperscript{16,17} Moreover, UV radiation was more likely a risk factor of
<table>
<thead>
<tr>
<th>Factors</th>
<th>Association</th>
<th>IIM Phenotypes</th>
<th>MSAs</th>
<th>Genetic Factors</th>
<th>Evidence from</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV radiation</td>
<td>Risk</td>
<td>DM</td>
<td>Anti-Mi2</td>
<td></td>
<td>4,15–17</td>
</tr>
<tr>
<td>Smoking</td>
<td>Risk</td>
<td>PM</td>
<td>Anti-Jo1</td>
<td>HLA-DRB1*03:01</td>
<td>19–21</td>
</tr>
<tr>
<td></td>
<td>Protective</td>
<td></td>
<td>Anti-TIF1γ</td>
<td>HLA-DRB1*03:01</td>
<td></td>
</tr>
<tr>
<td>Pollutants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silica</td>
<td>Risk</td>
<td>DMb</td>
<td>Anti-Jo1a</td>
<td></td>
<td>9,23</td>
</tr>
<tr>
<td>Inorganic dust</td>
<td>Risk</td>
<td>IIMb</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Dust, gas, fume</td>
<td>Risk</td>
<td>ASSD</td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>World Trade Center dust</td>
<td>Risk</td>
<td>DM/PMb</td>
<td>Anti-Jo1a</td>
<td></td>
<td>26,27</td>
</tr>
<tr>
<td>Infectious agents</td>
<td>Risk</td>
<td>DM, ASSD, IMNM, IBM, PM</td>
<td>Anti-TIF1γc</td>
<td>HLA-DRB1*11:01</td>
<td>11,12,34–38,42–44</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Risk</td>
<td>IMNM, DM, PM</td>
<td>Anti-HMGCR</td>
<td>HLA-DRB1*11:01</td>
<td>34,47,48,52,54,59,61</td>
</tr>
<tr>
<td>Immune checkpoint inhibitors</td>
<td>Risk</td>
<td>IIM</td>
<td>Anti-Jo1</td>
<td></td>
<td>63–66</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>Risk</td>
<td>IIM</td>
<td>Anti-Mi2</td>
<td></td>
<td>68,69</td>
</tr>
</tbody>
</table>

Abbreviations: ASSD, antisynthetase syndrome; DM, dermatomyositis; HLA-DRB1, major histocompatibility complex, class II, DR beta 1; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; MDA5, melanoma differentiation-associated gene 5; MSAs, myositis-specific autoantibodies; PM, polymyositis; TIF1γ, transcriptional intermediary factor 1γ; UV, ultraviolet.

a Based on descriptive data.

b Evidence from combined analyses including other autoimmune diseases.

c Based on serologic data.
DM and anti-Mi2 autoantibodies in Caucasian populations than in non-Caucasian populations. The absence of associations in men and in non-Caucasian populations could be due to small sample size because most patients included were women and Caucasians.

It is not fully known how UV radiation may trigger the onset of DM but there are findings showing upregulation of the Mi2 protein but not the other subunits of the nucleosome remodeling and deacetylase complex in keratinocytes shortly after 30 minutes exposure to UV treatment. In addition, upregulations of Mi2 protein after UV exposure were also noted in several cancer cell types. In addition, ionizing radiation that cause DNA damage could also result in rapid accumulation of Mi2 protein. These findings combined suggest that UV radiation may contribute to the development of DM by causing DNA damage and by increasing antigen presentation in the affected cells.

**Smoking**

Smoking has been found to confer an increased risk for anti-Jo1 autoantibodies in particular in genetically susceptible individuals with IIM. Anti-Jo1 positive patients were more likely to have a smoking history than anti-Jo1 negative patients. Smokers with IIM carrying allele in the major histocompatibility complex, class II, DR beta 1 gene (HLA-DRB1*03) had the greatest risk of anti-Jo1 autoantibody positivity compared with other combinations of smoking history and positivity of anti-Jo1 autoantibodies among patients with IIM. Consistent findings were noted in the analysis stratified by sex but women had a stronger association than men. A follow-up study with higher resolution imputation data found an even stronger association between anti-Jo1 autoantibodies and smoking in HLA-DRBI*03:01 positive patients. Interactions on the multiplicative scale between HLA-DRB1*03/*03:01 allele and smoking when modeling the risk of anti-Jo1 autoantibodies has been tested without significant interaction, potentially due to lack of power. It has also been suggested that the association between smoking and anti-Jo1 autoantibodies could be independent of HLA-DRB1*03:01. Together, these findings indicate that smoking is a risk factor of developing the anti-Jo1 autoantibodies and confers an additional risk in patients carrying HLA-DRB1*03:01 allele.

There is a study analyzing smoking in pack-years and reporting that the likelihood was increased by 2% for PM and IIM-associated interstitial lung disease (ILD) and by 1% for anti-Jo1 autoantibodies but was decreased by 7% for anti-transcriptional intermediary factor 1 α/γ (TIF1α/γ) autoantibodies for every increased unit of pack-years. However, the estimate for anti-Jo1 autoantibodies was not statistically significant. Similar associations were observed in the analyses including only Caucasian patients while no significant associations were noted in African American patients, probably due to a smaller number of patients. Importantly, this study also revealed that smoking had the strongest positive associations with PM, ILD, and anti-Jo1 autoantibodies, as well as a greatest inverse association with anti-TIF1α/γ autoantibodies in patients with HLA-DRB1*03:01 allele.

In summary, although lack of evidence from studies with longitudinal data raises uncertainty of a causal link between smoking and IIM, observational data support that smoking may have a role in the pathogenesis of anti-Jo1 positive IIM, potentially by triggering the development of anti-Jo1 autoantibodies in susceptible individuals carrying HLA-DRB1*03:01 allele.

**Pollutants**

A wide range of environmental pollutants has been reported to potentially trigger the onset of IIM. Earlier case series found that some DM patients had long-term
occupational exposure to silica or organic solvents before disease onset.\textsuperscript{22,23} The association between silica and DM has been examined further in a Swedish cohort study including 241,077 men employed in the construction industry.\textsuperscript{9} This study revealed that the risk of developing systemic lupus erythematosus, systemic sclerosis (SSc), or DM was almost doubled in workers exposed to silica dust compared with those unexposed office workers after controlling for age and smoking.\textsuperscript{9} A recent study including 438,068 US discharge military veterans found that the odds of SSc, vasculitis, or IIM was significantly increased by 23\% for those exposed to inorganic dust during services in Afghanistan or in Iraq than those unexposed after adjusting for age, sex, race, and smoking status, and the association became stronger as the length of service was increased.\textsuperscript{10}

There is more evidence supporting a role of occupational pollutants in the pathogenesis of ASSD compared with other IIM phenotypes although findings are based on self-reported case-control data, and might therefore be subject to recall bias,\textsuperscript{24} and some more descriptive data.\textsuperscript{23,25–28} A case-control study observed a significantly higher frequency of lifetime occupational exposure to dust, gases, or fumes in 32 patients with ASSD (n = 25) or ILD (n = 7) than 32 IIM patients without ASSD (50\% vs 22\%).\textsuperscript{24} Moreover, patients with ASSD with high occupational exposure (94\%) were more likely to have ILD than those exposed to no or low occupational pollutants (75\%).\textsuperscript{24} Furthermore, a high likelihood of anti-Jo1 autoantibody positivity was observed in several studies investigating the association between environmental exposure and risk of autoimmune diseases. Both acute and chronic exposures to aerosolized World Trade Center dust after the 9/11 attack in firefighters were associated with increased risk of autoimmune diseases.\textsuperscript{26} Among the identified autoimmune diseases, there were 8 cases of DM/PM and 2 of them were positive to anti-Jo1 autoantibodies.\textsuperscript{26,27} In a study of 10 patients with ASSD, 6 had hypersensitivity pneumonitis preceding the onset of ASSD, 9 were exposed to significant levels of domiciliary exposures including mold, birds, pigeon and feather pillow, and 6 were anti-Jo1 positive.\textsuperscript{28} One of the 3 patients with silica-associated DM was with the presence of anti-Jo1 autoantibodies.\textsuperscript{23} These findings suggest a triggering role of environmental pollutants in onset of autoimmunity, perhaps in lungs, which may result in systemic onset of autoimmunity later affecting other tissues.

\textbf{Infectious Agents}

Seasonality of birth or IIM disease onset observed in several studies suggests a nonrandom disease development, which may be affected by environmental exposures with a seasonal pattern such as infectious agents.\textsuperscript{29–32} For example, there are studies reporting aggregations of disease onset of patients with antimelanoma differentiation-associated gene 5 (MDA5) autoantibodies in winter where flu season coincided.\textsuperscript{29,30,33} However, no causal inference could be drawn from these seasonal patterns.

The role of infectious agents in pathogenesis of IIM implicated by seasonality is further supported by the epidemiologic findings of preceding infections in patients with IIM. A nationwide cohort study in Denmark noted that the risk of DM/PM in individuals with history of hospital contact for viral, bacterial, and other infections was significantly increased and was 2-fold higher than those without hospital contact for infections after adjusting for calendar year, sex and its interaction with age, and comorbidities.\textsuperscript{11} Furthermore, this association was strengthened when the number of hospitalizations increased and as the time since hospitalization with an infection to diagnosis of DM/PM decreased.\textsuperscript{11} These findings are in line with the results of 2 case-control studies.\textsuperscript{12,34} In one of the studies, the risk of reverse causality was
minimized by excluding infections diagnosed in the year of IIM diagnosis. Specifically, the types of infections associated with IIM were mainly respiratory and gastrointestinal infections. 

Serologic evidence suggests that the link between previous infection and IIM may be attributable to certain microbial agents, particularly viruses. Higher titers of antibodies against hepatitis C virus, Epstein-Barr virus (EBV), influenza A and B, parainfluenza, coxsackie virus, or cytomegalovirus (CMV) in patients with IIM than in controls were observed in several studies. A recent case-control study also found that antibodies against viral families of Coronaviridae, Geminiviridae, Herpesviridae, Orthomyxoviridae, and Poxviridae in adult patients with anti-TIF1γ autoantibodies were enriched, whereas the enriched viral families in matched healthy controls were Picornaviridae, Caliciviridae, Orthomyxoviridae, Coronaviridae, and Retroviridae. Specifically, a previous study found that, in comparison to matched healthy controls, patients with PM had higher levels of immunoglobulin M (IgM) and immunoglobulin G (IgG) against EBV, and IgM against CMV. Interestingly, infiltrates of CD4+ CD28null T cells in muscle biopsies of patients with DM has been found solely in patients with IgG against CMV and not in patients without. Although no causality between these viral species and onset of IIM can be drawn from these serologic findings, they support the hypothesis for a role of acute (IgM) or latent (IgG) infection in the development of IIM.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has also been suggested as a trigger of IIM. The evidence supporting this assumption is weak, and includes the presence of DM-specific autoantibodies including anti-MDA5 and antinuclear matrix protein 2 autoantibodies in patients with coronavirus diseases 19 (COVID-19), and a remarkable similarity of pathophysiological features between autoimmune anti-MDA5 syndrome and COVID-19 and onset of the DM subgroup presenting with anti-MDA5 autoantibodies. However, acute-onset IIM related to COVID-19 could be a transient epiphenomenon. Future studies with longer follow-up time are warranted to evaluate if COVID-19 is associated with chronic IIM evolved from acute IIM.

It is still unclear how microbes may trigger the onset of IIM but the abovementioned observations suggest a potential linkage to lung involvement in IIM. The elevated risks of ASSD on exposure to pneumonia, of ILD in patients with IIM exposed to pneumonia, tuberculosis, or sarcoidosis observed, respectively, in 2 studies further support this hypothesis. Molecular mimicry may be a mechanism involved in the onset of autoimmunity because shared epitope sequences have been observed between variola virus and tripartite motif-containing protein 3, which shared high sequence identity with TIF1γ, and between 3 immunogenic linear epitopes derived from patients with DM and SARS-CoV-2 proteins.

Medications

**Statin**

Statins are drugs widely used for reducing the risk of cardiovascular diseases by binding to 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) and thus interfering in the cholesterol biosynthesis. Discontinuation due to associated adverse events including muscle toxicity is common. Statin-induced myopathy usually resolves after discontinuation but when the symptoms persist and require immunomodulatory treatment, statin-associated autoimmune IIM may have developed.

Among all the IIM phenotypes, IMNM with anti-HMGCR autoantibodies is strongly related to statin exposure; up to 67% of patients from North America were exposed to statins before disease onset. Moreover, compared with IMNM patients with
anti-signal recognition particle autoantibodies, patients with anti-HMGCR autoantibodies were 33-fold more likely to have history of statin use.\textsuperscript{59} Unlike patients from North America, statin exposure in anti-HMGCR positive IMNM patients from eastern countries is much lower, ranging from 15\% to 38\%.\textsuperscript{60,61} Because naturally occurring HMGCR inhibitors have been found in dietary products commonly used in eastern cuisine,\textsuperscript{62,63} this discrepancy may suggest an association between natural sources of HMGCR inhibitors and anti-HMGCR positive IMNM. Indeed, this assumption has been supported by 2 cases of statin naïve anti-HMGCR positive patients with consumption of shiitake mushroom and red rice, respectively.\textsuperscript{64,65} However, there is lack of supportive evidence from epidemiologic studies and the mechanisms of how these dietary compounds can inhibit the activity of HMGCR are unknown, similarly how they can lead to the production of anti-HMGCR autoantibodies.

Statins may also be a risk factor for other IIM phenotypes, although evidence show weaker associations to other subsets than to IMNM. In a study exclusively including patients with DM or PM but not IMNM, the odds of regular statin use 6 months before disease onset in these patients was 6 times higher than the age-matched and sex-matched controls.\textsuperscript{52} This finding was reproduced in a case-control study comparing patients with biopsy confirmed IIM excluding IMNM to age-matched and sex-matched controls, although the association was weaker than that observed in anti-HMGCR-positive patients.\textsuperscript{54,59} Another case-control study reported that patients with DM and patients with PM were 2 times more likely to be exposed to statin use a year before disease diagnosis than patients with IBM after adjusting for age, gender, race, and year of diagnosis.\textsuperscript{54}

It has been suggested that statins contribute to the pathogenesis of IIM by upregulating HMGCR in regenerating muscle cells.\textsuperscript{66} If self-tolerance is lost to HMGCR, production of anti-HMGCR autoantibodies will be initiated, contributing to autoimmunity attacking muscle tissue. Individuals carrying the genetic variant \textit{HLA-DR11} may be more susceptible to this mechanism because this variant has been found to be strongly associated with statin-induced IMNM who are anti-HMGCR positive.\textsuperscript{67} This evidence supports a role of the adaptive immune system in this subset of IIM. Other proinflammatory effects related to statins such as increased expression of major histocompatibility complex class I in myofibers may be involved in the disease development as well.\textsuperscript{47,56}

Little is known what nongenetic factors are related to statin-associated autoimmune IIM. Characteristics such as older age, female sex, chronic statin exposure, and comorbidities including Type 2 diabetes, hypertension, and hyperlipidemia have frequently been reported in cases of statin-associated autoimmune IIM.\textsuperscript{47–49,51,52,55,58,68} Interestingly, patients with prior exposure to simvastatin or pravastatin were at higher risk of having chronic muscular diseases including DM and PM than patients exposed to atorvastatin or fluvastatin but the associations were not statistically significant.\textsuperscript{52} Significant interaction between statins and proton pump inhibitors was also found when estimating the odds ratio of statin-associated DM or PM.\textsuperscript{52}

The association between statins and IMNM has led to a safety concern about statin use in patients with IIM for cardiovascular disease prevention. Although evidence is sparse, a study observed that 22 out of 23 patients with non-HMGCR IIM tolerated statins well.\textsuperscript{57}

\textit{Immune checkpoint inhibitors}

Immune checkpoint inhibitors (ICIs) are a group of medications that have revolutionized cancer treatment in recent years. Because they interfere with immune pathways,
they have been associated with rheumatic immune-related adverse events, for example, myositis. Symptoms typically occur shortly after monotherapy or combination therapy with programmed death (PD)-1/PD-ligand 1 inhibitor or/and cytotoxic T lymphocyte antigen-4 inhibitor. 69–72 The pathogenesis of ICI-associated myositis is not well-understood but enhanced activation of T cells may partially explain the phenomenon because antigen-specific T cells play an important role in IIM development. 1,73 Importantly, even though lymphocytic infiltration is presented in muscle biopsy of patients with ICI-associated myositis, 69 characteristics such as concurrence with myasthenia gravis or myocarditis, infrequent positivity of MSAs/MAAs, high mortality, and resolution after steroid and intravenous immunoglobin treatments highlight a distinct pathologic mechanism different from that of IIM. 69,71,72

**Vitamin D Deficiency**

Vitamin D deficiency has been suggested as a risk factor for adult IIM. Previous evidence has shown that vitamin D deficiency was not only more commonly seen in patients with newly diagnosed IIM than matched controls; it was also correlated with elevated muscle enzymes, increased number of proinflammatory cells, as well as anti-Jo1 and anti-Mi2 autoantibodies in newly diagnosed and untreated patients with IIM. 74,75 Heliotrope rash, gastrointestinal and liver involvements were also frequently seen in patients with IIM with extremely low levels of vitamin D at diagnosis. 74 Interestingly, vitamin D receptor polymorphisms associated with IIM have been suggested but these findings are inconsistent. 76,77 Given that only one time-point measurement of vitamin D was analyzed and that the observed low level at IIM diagnosis can be due to less outdoor activity because of muscle weakness, it remains unclear if vitamin D deficiency is causally associated with IIM.

**SUMMARY**

In this review, we have discussed several suggested environmental factors and their influence on clinically or serologically defined IIM phenotypes. This knowledge provides important clues to infer into the pathogenic mechanisms of IIM. Importantly, there is a growing body of evidence implicating lungs as the initial site of autoimmunity, which later may lead to the onset of some subsets of IIM in particular those with ILD. 78,79 As presented above, many of the external environmental factors suggested as risk factors for IIM, including smoking, occupational pollutants, and infectious agents, are associated with the subtype ASSD, IIM-associated ILD, or the presence of either anti-Jo1 or anti-MDA5 autoantibodies, 10,20,34,44,80 which are features of lung involvement in IIM. These observations further support that autoimmunity of IIM may first take place in lungs in response to environmental insults in susceptible individuals. Furthermore, the links to specific MSAs provide insight into the site of antigen presentation and production of autoantibodies, as seen in anti-Jo1, anti-Mi2, and anti-HMGCR autoantibodies. 18,66,81 The dose-dependent manners of correlations found in smoking, occupational dust, infections, and vitamin D deficiency suggest proportional correlations between accumulation of environmental exposure and IIM onset. 10,11,21,74 Besides pathogenic implications, information on environmental factors for IIM and IIM-related complications is useful for disease prevention and management.

**FUTURE DIRECTIONS**

Although several attempts have been made to identify potential environmental factors associated with IIM, no causal relationship has been established for a single factor.
Given the fact that IIM is a complex and rare disease, this is not surprising. Small sample size, lack of valid and longitudinal data on environmental exposure and potential confounders, as well as lack of proper control groups, confounding adjustment, and analysis by serologic profile are common limitations of many of the previously published studies, and these also reflect the challenges for future studies. It is impossible to overcome all these limitations in one study but establishing international collaborations to increase sample size and data diversity, and to enable standardized data collection and proper selection of controls is crucial to explore the role of environmental factors in the development of IIM. Moreover, although the pathogenesis of IIM is multifactorial, it is interesting that previous studies seldom considered interactions between environmental factors or between environmental and genetic factors. There is also a lack of mechanistic studies exploring the role of environmental factors for IIM at molecular level. Future epidemiologic and basic science studies should focus on answering these questions.

CLINICS CARE POINTS

- Little is currently known about the clinical relevance of avoiding the suggested environmental triggers in patients with idiopathic inflammatory myopathies (IIMs). However, in clinical practice, patients with dermatomyositis are recommended to protect skin from sun exposure.
- Although smoking cessation is recommended for general long-term health benefits, we suggest all providers counsel patients on smoking cessation after IIM diagnosis.
- Current evidence suggests that statin use as secondary cardiovascular prophylaxis is safe and tolerable for patients with non-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase IIM.

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DISCLOSURE

Dr I.E. Lundberg has received consulting fees from Corbus Pharmaceuticals, Inc and research grants from AstraZeneca and has been serving on the advisory board for Astra Zeneca, Bristol Myers Squibb, EMD Serono Research & Development Institute, Argenx, Octapharma, Kezaar, Orphazyme, Pfizer and Janssen and has stock shares in Roche and Novartis. The other authors declare no conflicts of interest.

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