Changing Indoor Microbial Environments to Benefit Human Health: What Do We Know?

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Indoor environments are known to affect human health in many ways.
This presentation will very briefly review available findings on a number of relationships.

**ENVIRONMENTAL factors** (microbially-related)

**ADVERSE HEALTH effects**

**BENEFICIAL HEALTH effects**

**Measured MICROBIAL TAXA/COMPOUNDS**

**Measured MICROBIAL COMMUNITY FACTORS**
Environment factors (microbial-related) → adverse human health effects

- Observed dampness or mold → increased respiratory and allergic disease
  - Removal of dampness and mold → decreased health effects
  - if observed dampness/mold, ventilation (relatively dry outdoor air)* → decreased health effects
- Lower measured wall moisture → decreased asthma risk
- Disease transmitted from other occupants
  - From surfaces → more resp and GI infections
    - Cleaning/disinfection → reduces transmission
  - By aerosols → more resp infections
    - Increased ventilation, air filtration -→ reduces transmission only of long-range airborne
- (Non-farm environments . . .)

* This dilutes microbial exposures. Caution: increased ventilation with moist outdoor air may increase indoor dampness/mold.
Much evidence links “observed” indoor dampness or mold* to specific health effects

Do you see it or smell it?

<table>
<thead>
<tr>
<th>Health Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IOM 2004</td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td>●</td>
</tr>
<tr>
<td>Asthma development (new)</td>
<td>●</td>
</tr>
<tr>
<td>Asthma, current</td>
<td>●</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>●</td>
</tr>
<tr>
<td>Eczema</td>
<td>●</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>●</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>●</td>
</tr>
<tr>
<td>Wheeze</td>
<td>●</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>●</td>
</tr>
<tr>
<td>Cough</td>
<td>●</td>
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<tr>
<td>Upper resp tract symptoms</td>
<td>●</td>
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</tbody>
</table>

*Observed Dampness or Mold:

- Visible mold
- Mold odor
- Moisture/dampness
- Water damage

Key

- ● Sufficient evidence for causation
- ○ Sufficient evidence for association
- ○ Limited or suggestive evidence for association
- --- Not assessed
Observed dampness and mold are consistently linked to increased risks for multiple respiratory and allergic effects.

- **Asthma exacerbation**
- **Asthma development**
- **Respiratory infections**
- **Allergic rhinitis**
- **Eczema**

Lack of consistent associations with microbial measurements not understood.

- **Specific causal agent(s) not identified**

- **Allergic and non-allergic mechanisms likely**

- **Per available evidence, remediating observed D/M is beneficial to health**

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**Do you see it or smell it?**

**Evident dampness or mold**

**Measured microbial factors**
Example: A 3-level index of visible mold and water damage was strongly dose-related to respiratory effects, in 4 analyses

![Bar chart showing Dampness/Mold Index Levels (four studies)](image)

- **No Dampness/Mold**
  - No D/M indicators:
    - water damage
    - visible mold
    - mold odor
    - history of visible mold or water damage

- **Low Dampness/Mold**
  - At least 1 of 4 indicators, but below size thresholds for HIGH

- **High Dampness/Mold**
  - Visible mold ≥0.2 m² in one room OR visible mold + water damage ≥0.2 m² on one surface

**NOTE:**
- wheeze + atopy – both compared to neither;
- wheeze if atopy – wheeze vs. none, only among atopic subjects
BUT: Farm environments have consistent beneficial effects, protecting children from developing asthma and allergy.
We do not understand the specific exposures or mechanisms related to effects of D/M or farm environments.
Farm environments → beneficial health effects: proposed mediators

- **Traditional farming environments:** specific beneficial factors (in utero or early childhood) reduce asthma, atopy, hay fever . . .
  - Animal sheds, stables, cattle, pig-keeping, number of different animal species
  - Hay, hay lofts, silage (paradox)
  - Grain and associated activities
  - Farm milk (drinking unpasteurized)
  - Large family (independent of farming)

- **Farm house dust** reproduces effects in mice (unless no immune signaling molecules)\(^1\)

- **Low-dose endotoxin** may be a key factor\(^2\)
  - Same effects as farm dust in mice (unless x’ed A20)
  - Reduces lung cytokines that lead (thru induced A20 enzyme) to type 2 immunity/sensitization

\(^1\) Stein 2016 NEJM 375:411-21;  \(^2\) Schuijs 2015 Science 349:1105-10
Non-farm environments ➔ beneficial health effects

- Dog exposure in early infancy ➔ altered house dust ➔ altered gut microbiome including *Lactobacillus johnsonii*, which protected mice against respiratory allergen challenge and viral infection and improved immune parameters\(^1\)
- Less developed countries ➔ more matured immune response in infants\(^2\)
- Neither personal or home cleanliness ➔ risk of asthma or allergies (but did influence dust parameters)\(^3\)
- Non-air-conditioned office buildings ➔ reduced building-related respiratory and other symptoms\(^4\)

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Environmental factors $\rightarrow$ indoor microbial communities

- Living on farms $\rightarrow$ greater microbial diversity$^{1,2}$
- Pets or dogs indoors $\rightarrow$ greater bacterial diversity and higher relative abundance of dog-associated taxa$^{3,4}$
- Suburban vs. urban, leaks, wall moisture, flooding, longer AC use $\rightarrow$ greater fungal richness$^{4,5,6}$
- Higher outdoor ventilation rate reduced relative abundance of human pathogen-like bacteria$^{7}$

1 Birzele 2016 Allergy (advance E-pub); 2 Stein 2016 NEJM 375:411-21
3 Dunn 2013 8:e64133; 4 Dannemiller 2016 Indoor Air 26:179-92
Environmental factors ➔ measured indoor microbial taxa

- Living on farms ➔ higher endotoxin\(^1\)
- Farming ➔ in dust, *Clostridium* *spp*, *Facklamia* *spp*, *Ruminococcaceae* (family), and others\(^2\)
- Greater occupant density ➔ *Lactobacillus johnsonii* and other beneficial taxa\(^3\)
- Specific human microbiota ➔ predominant influence on occupied home microbiome\(^4\)

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\(^1\) Stein 2016 NEJM 375:411-21; \(^2\) Birzele 2016 Allergy (advance E-pub);
\(^3\) Dannemiller 2016 Indoor Air 26:179-92; \(^4\) Lax 2014 Science 345:1048-52
Measured indoor microbial factors (community/taxa/compounds) $\rightarrow$ adverse health effects

- Low bacterial diversity e.g.,\(^1\)
- High bacterial richness\(^2\)

- (No specific taxa yet consistently linked)
- Hydrophilic fungi (QPCR, culture) $\rightarrow$ asthma\(^3,4\)
- *Penicillium* and total fungi in air (culture) $\rightarrow$ asthma exacerbation\(^5\)
- Summed allergenic fungal species, total fungi and *Volutella spp* (fungus) concentrations $\rightarrow$ asthma severity\(^1\)
- Endotoxin, glucan $\rightarrow$ wheeze\(^6\) (but also beneficial)
- Muramic acid (Gram-positive bacteria) $\rightarrow$ in mice, increased immunotoxic potential\(^7\)

\(^1\) Ege 2011 NEJM 364:701-9; \(^2\) Dannemiller 2016 JACI 138:76-83; \(^3\) Reponen 2012 JACI 130:639-44; \(^4\) Park 2008 EHP 116:45-50; \(^5\) Kanchongkittiphon 2015 EHP 123:6; \(^6\) Mendell 2011 EHP 119:748-756; \(^7\) Huttunen 2016 Indoor Air 26:380-390
Measured indoor microbial factors (community or taxa) $\rightarrow$ beneficial health effects (= reduced asthma/allergy/wheeze)

- Greater microbial diversity$^{1,2,3,4}$
- Index of farm-like bacteria (explained entire farm effect)!$^{5}$
- Specific bacteria
  - *Listeria monocytogenes, Bacillus spp, Corynebacterium spp; Acinetobacter spp, Lactobacillus spp, Neisseria spp, Staphylococcus sciuri, Jeotgalicoccus spp, Corynebacterium spp, Firmicutes and Bacteriodetes; Mycobacterium spp, Bifidobacteriacaea spp, Clostridium spp*$^{1,3,6,7}$
- Specific fungi
  - *P chrysogenum, Pseudotaeniolina globose; Eurotium; Aureobasidium pallulans, Penicillum and Aspergillus spp.$^{1,4,8,9,10}$
- Glucans, endotoxin, muramic acid$^{11,12}$ (but also adverse!)
- Total microbial markers$^{13}$

Currently known biologic mechanisms cannot explain the epidemiologic observations

- **Some** early microbial exposures **reduce** later atopy and asthma
  - can also **increase wheeze**¹
- **But** dampness/mold consistently **increase** respiratory risks in infants, children, and adults² (so not all early microbial exposures good)

¹ Celedon 2007 JACI 120;120:144-9; ² Mendell 2011 EHP 119;748-56
Positive and adverse effects from indoor microbial exposures are likely to be through different mechanisms

- **Dampness/mold**
  - Specific sensitization by antigens, for atopic
  - Pro-inflammatory effects of microbial compounds (e.g., glucans, endotoxin . . . ) in non-atopic and atopic

- **Farms and beneficial exposures (animals, feed, dogs, children)**
  - General benefit of diverse microbial exposures?
  - Specific beneficial taxa or microbial compounds?
  - Positive influence on developing immune system\(^1\)
  - May involve changes in human gut/lung microbiome

\(^1\) von Mutius 2016 JACI;137:680-9
## Summary: Microbial factors and exposures in buildings and associated health effects

<table>
<thead>
<tr>
<th>Environmental Influence</th>
<th>Health Effects</th>
<th>Specific Microbial Agents?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoor Dampness or Mold (observed)</td>
<td>Increased new asthma, asthma exacerbation, allergic rhinitis, respiratory infections</td>
<td>Not determined, possibly: hydrophilic fungi, beta glucans; (bacteria $\rightarrow$) endotoxin, muramic acid</td>
</tr>
<tr>
<td>Presence of air conditioning systems in offices</td>
<td>Increased Building-related symptoms (sick building syndrome), especially breathing symptoms</td>
<td>Not definite that microbially caused, but inapparent microbial growth on cooling coils seems most likely cause</td>
</tr>
<tr>
<td>Disease Agents on indoor surfaces</td>
<td>Increased respiratory and gastrointestinal infections</td>
<td>Virus and bacteria; e.g., Norwalk virus, Staphylococcus aureus, influenza virus, rhinovirus</td>
</tr>
<tr>
<td>Disease Agents in indoor air</td>
<td>Increased respiratory infections (illness absence)</td>
<td>Virus and bacteria; e.g., influenza virus, rhinovirus, tuberculosis</td>
</tr>
<tr>
<td>Lack of diverse microbial exposures</td>
<td>Increased asthma and allergy</td>
<td>Less diverse bacterial and fungal communities</td>
</tr>
<tr>
<td>Lack of farm-like environment (animals, feed)</td>
<td>Increased asthma and allergy</td>
<td>Lack of specific animal-associated and feed-associated bacteria (and fungi)</td>
</tr>
</tbody>
</table>
Intentionally making the indoor environment and microbiome healthier for occupants will be challenging

- Document causation (difficult) before designing interventions?
- Benefits from diversity or from specific unusual exposures?
- Target optimal ages?
- Is the human microbiome the ultimate target?
- In changing building design, materials, operation or maintenance:
  - Reduce adverse exposures (D/M)?
  - Increase beneficial exposures?
- Difficult to identify/provide all missing beneficial factors
- Best to create self-sustaining beneficial processes (e.g., as with human fecal transplants)
Available knowledge suggests intervention ideas for changing indoor microbiomes to improve health

<table>
<thead>
<tr>
<th>Environmental Influence</th>
<th>Potential Intervention</th>
<th>Strength of Evidence</th>
</tr>
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</table>
| Indoor Dampness or Mold → allergic, respiratory, and infectious disease | • Remove moisture source  
• Dry/remove wet materials  
• Clean/remove moldy materials  
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• if D/M observed, increase ventilation with relatively dry outdoor air* to dilute microbial exposures | Accepted current practices (much observational evidence + 1 intervention study, but limited data)  
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Limited/suggestive evidence (3 observational studies) |
| Presence of air-conditioning systems in offices → building-related symptoms | • (GUV irradiation of air-conditioning cooling coils?) | Much evidence of observed correlation; limited intervention evidence (1 study) of microbial causality and GUV efficacy |
| Disease Agents on indoor surfaces → respiratory or gastrointestinal infections | • Clean/disinfect often-touched surfaces (current anti-bacterial products ineffective) | Accepted current practice |
| Disease Agents in indoor air → infectious respiratory disease | • Isolation  
• Increased outdoor air ventilation  
• Increased particle filtration in recirculation | Accepted current practices in health care settings; Limited/suggestive evidence for general buildings |
| Lack of diverse microbial exposures → asthma/ allergy | (Add diverse microbial cocktail??) | Limited, observed correlations only |
| Lack of farm-like environment (animals, feed) → asthma or allergy | (Add farm-like microbial cocktail??)  
(Barn-fecal transplants to homes??)  
(Barn/home carpet rotation cycle??)  
(Indoor cattle, pigs as pets??)  
(Hay-based furniture??) | Limited, observed correlations only |

* Caution: increased ventilation with moist outdoor air can increase indoor dampness/mold
Questions?