Uncontrolled asthma occurs in all GINA treatment steps and is associated with worse physical health – a report from the OLIN adult asthma cohort

Caroline Stridsman, Malin Axelsson, Katja Warm & Helena Backman

To cite this article: Caroline Stridsman, Malin Axelsson, Katja Warm & Helena Backman (2020): Uncontrolled asthma occurs in all GINA treatment steps and is associated with worse physical health – a report from the OLIN adult asthma cohort, Journal of Asthma, DOI: 10.1080/02770903.2020.1713150

To link to this article: https://doi.org/10.1080/02770903.2020.1713150

© 2020 The Author(s). Published with license by Taylor and Francis Group, LLC

Accepted author version posted online: 07 Jan 2020.
Published online: 14 Jan 2020.

Submit your article to this journal

Article views: 507

View related articles

View Crossmark data
Uncontrolled asthma occurs in all GINA treatment steps and is associated with worse physical health – a report from the OLIN adult asthma cohort

Caroline Stridsman, RN, PhD\textsuperscript{a,b}, Malin Axelsson, RN\textsuperscript{c}, Katja Warm, MD, PhD\textsuperscript{b}, and Helena Backman, PhD\textsuperscript{d}

\textsuperscript{a}Division of Nursing, Department of Health Sciences, Luleå University of Technology, Luleå, Sweden; \textsuperscript{b}Section of Medicine, The OLIN Unit, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; \textsuperscript{c}Department of Care Sciences, Faculty of Health and Society, Malmö University, Malmö, Sweden; \textsuperscript{d}Section of Sustainable Health, The OLIN Unit, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

**ABSTRACT**

**Objective:** To study asthma exacerbations, healthcare utilization and health status among subjects with asthma with different treatment regimens and levels of asthma control.

**Methods:** In 2012–2014, \(n=1425\) adults from a population-based asthma cohort within the OLIN studies (Obstructive Lung disease in Northern Sweden) were invited to a follow-up including spirometry and a structured interview, \(n=1006\) participated. Asthma Control Test (ACT) was used to detect uncontrolled asthma, and physical and mental dimensions of health were measured with SF-8. Pharmacological treatment use was classified by Global Initiative for Asthma treatment steps. Out of \(n=830\) with current asthma, \(n=714\) answered ACT (57% women, 32–92 years) and were included in the study.

**Results:** Uncontrolled asthma increased per treatment step (no treatment 9.9%, treatment step 1–3 24.1%, and treatment steps 4–5 39.9%, \(p<0.001\)). A higher proportion of subjects with uncontrolled asthma reported exacerbations, healthcare utilization, and worse health status than those with controlled asthma. The proportion of subjects reporting exacerbations, healthcare visits, emergency room visits and regular follow-up visits increased per treatment step. Worse health was associated with uncontrolled asthma, but not with the level of treatment. A higher proportion of women than men reported exacerbations, any healthcare visits, and lower health. Regular follow-up visits to a physician were uncommon (women 21.2% vs. men 14.6%, \(p=0.022\)).

**Conclusions:** Uncontrolled asthma is common in all treatment steps, and is associated with worse health status. However, health status did not differ by treatment steps. Identifying subjects with uncontrolled asthma regardless of treatment regimens should be a priority, thus follow-up visits are important.

**Introduction**

Asthma is a chronic disease that imposes a substantial burden in terms of costs both for society and individuals (1). The most important cost drivers are work and school absence, medications, and hospitalizations (2,3). The prevalence of asthma is still increasing in some countries (4), estimated to be 4–10% among adults (4–6) and higher among women than men (4,7). The Global Initiative for Asthma (GINA) treatment strategy is used worldwide in asthma management, and is based on a step-wise approach; step 1 (low dose treatment for mild asthma) to step 5 (high dose treatment for severe asthma). The treatment should be personalized and regularly adjusted in relation to the patient’s needs (1).

Poor asthma control may lead to decreased health status (8–10), exacerbations (11,12), and increased healthcare costs (9). The level of asthma control can easily be detected by different instruments (13,14), and a poor asthma control can be related to low adherence to asthma treatment or incorrect inhalation technique. However, if both adherence and inhalation technique is confirmed, and the patient still has poor asthma control, step-up treatment should be considered (11). About 5% of all asthmatics have severe asthma (15,16), and these are subjects that remain

ARTICLE HISTORY

Received 4 October 2019
Revised 3 January 2020
Accepted 5 January 2020

KEYWORDS

Epidemiology; management/control; quality of life; treatment

Copyright and Reprints (\copyright 2020 The Author(s)). Published with license by Taylor and Francis Group, LLC. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.
uncontrolled despite being stepped-up to high-dose treatment (treatment step 4 or 5), or subjects in need of high-dose treatment to prevent the disease from becoming uncontrolled (12,17).

Previous studies highlight that poor asthma control is common, and may lead to worse health outcomes (8–12). However, large population-based studies on adults with asthma, including detailed data about self-reported asthma treatment and associated health outcomes are rare. This study will generate knowledge about what pharmacological treatment subjects with asthma actually use, including those without current treatment. Thus, our aim was to study asthma exacerbations, healthcare utilization, and health status among subjects with asthma with different treatment regimens and levels of asthma control.

Material and methods

Study population

Within the Obstructive Lung disease in Northern Sweden (OLIN) studies, a population-based cohort of adults with asthma was recruited between the years 1986–2001 (n = 2,055). At study entry, the cohort included subjects reporting physician-diagnosed asthma, those reporting ever having had asthma and also those with a medical history of asthma along with physiologically verified bronchial variability or asthma medication (18). In 2012–2014, all subjects (n = 1,425) who were alive and still living in the county were invited to a clinical follow-up including pre- and post-bronchodilator spirometry, measurement of height and weight, blood sampling, and a detailed structured interview. Self-administrated questionnaires were used to assess asthma control and health status. N = 1,006 subjects participated (71% of invited), of which n = 830 had current asthma, and n = 714 completed the Asthma Control Test (ACT) and were further studied. The clinical follow-up has been described in detail including inclusion criteria at study entry and non-responder analysis (16,18). The study was approved by the Regional Ethical Board at Umeå University, Sweden, and all participants provided written informed consent (2011/106-31).

Questionnaires and examination

The structured interview consisted of questions about respiratory symptoms, smoking habits, exacerbations, pharmacological asthma treatment, and healthcare utilization. Asthma control was assessed using the validated ACT, which consists of five questions with responses on a 5-point scale. The sum of the score ranges from 5 to 25 and a lower score indicates poorer asthma control (13). ACT is recommended for use in clinical practice (11,17) and a score ≤19 indicates uncontrolled asthma (19). To assess generic health status, the self-administered eight-item Short-Form Health Survey (SF-8) was used. It is translated and validated for several different languages and has also a high reliability. The SF-8 produces two summary measures: the physical component summary (PCS) and the mental component summary (MCS), where a higher score indicates better health status (range 0–100) (20).

Definitions

Current asthma: Diagnosis of asthma in combination with at least one of asthma medication use, attacks of shortness of breath and/or any wheeze. Asthma treatment was classified according to GINA 2017 treatment steps (17). Treatment steps 1–3: Short-acting beta2 agonist (SABA) or long-acting beta2 agonist (LABA) without inhaled corticosteroids (ICS), ICS as-needed (periodically) regardless of dose level, or maintenance (most days/week) ICS low dose with or without LABA. Treatment steps 4–5: Maintenance medium to high dose ICS, and/or oral corticosteroids (OCS) maintenance or as-needed. No treatment: Not having any asthma medication. Asthma control: Uncontrolled asthma ACT ≤ 19, and controlled asthma ACT > 20. Asthma exacerbation: Treatment with antibiotics or oral corticosteroids (OCS) due to respiratory symptoms, asthma-related hospitalization or activity limitation or work absenteeism due to asthma for at least two successive days. Any healthcare visits: Healthcare utilization due to respiratory symptoms. Emergency room (ER) visits: Emergency healthcare utilization due to respiratory symptoms. Hospitalization: Hospitalized due to respiratory symptoms. All questions apply to the last 12 months.

Statistical analyses

The IBM Statistical Package for Social Sciences 24 (SPSS; IBM Corporation, Armonk, NY, USA) was used for statistical analyses. The Chi-square test was used to test for differences in proportions and the T-test or ANOVA for differences in means as appropriate. Linear by linear association assessed by Mantel-Haenszel test was used as test for trend. A p-values < 0.05 was considered statistically significant.
Results

Basic characteristics and asthma control by treatment step

Basic characteristics are presented in Table 1. Among the $n = 714$ participants, 56.0% were women, the mean age was 58.9 years, and approximately 25.0% had uncontrolled asthma. No asthma treatment was reported by 23.9%, while 51.1% were classified into treatment steps 1–3 and 24.9% into treatment steps 4–5. A significantly higher proportion of women than men were classified into treatment steps 1–3 and 4–5 (Table 1). The proportion of subjects with uncontrolled asthma increased significantly per treatment steps; no treatment 9.9%, treatment steps 1–3 24.1%, and treatment steps 4–5 39.9% (test for trend $p < 0.001$).

Asthma exacerbations

The proportion of subjects with exacerbations was 21.4%, and exacerbations were more common among women and among those with uncontrolled asthma. The proportion having exacerbations increased per treatment steps; 11.1% among those with no treatment, 18.1% in treatment steps 1–3, and 38.2% in treatment steps 4–5 ($p < 0.001$) (Table 2). Among those with uncontrolled asthma, the proportions with exacerbations were 23.5% among those with no treatment, 31.8% in treatment steps 1–3 and 52.1% in treatment steps 4–5 ($p = 0.013$) (Table 3).

Healthcare utilization due to respiratory symptoms

Any healthcare visits were reported by 29.1%, ER visits by 9.9%, and hospitalizations by 2.4%. A significantly higher proportion of women than men reported any healthcare visits, and the same trend was seen in ER visits, but not significantly so. Subjects with uncontrolled asthma had significantly more healthcare utilization than those with controlled asthma. Also, subjects with no treatment reported healthcare utilization due to respiratory symptoms, and the proportion of subjects with healthcare utilization increased per treatment step, but not significantly so regarding hospitalizations (Table 2). Among those with uncontrolled asthma, subjects with treatment steps 4–5 had the highest proportions of any healthcare visits (Table 3).

Regular follow-up visits to a physician or a nurse respectively, were reported by 18.3%, and 10.6% of the subjects. Follow-up visits to a physician were
more common among women than men, and among those with uncontrolled than controlled asthma. Follow-up visits to a nurse were slightly more common among those with uncontrolled than controlled asthma, but not significantly so. The proportion of subjects reporting regular follow-up visits increased by treatment step (Table 2). A higher proportion of subjects with exacerbations reported follow-up visits ≥1/year to a physician than those without exacerbations (34.6% vs. 13.9%, \( p < 0.001 \)).

**Physical and mental dimensions of health**

The mean physical and mental health scores were lower among women than men, and among those with uncontrolled asthma than among those with controlled asthma. No differences in physical or mental health were found by treatment steps (Tables 2 and 3). Both among subjects with no treatment at all, in treatment steps 1–3 and in treatment steps 4–5 respectively, the mean physical health score was lower among those with uncontrolled asthma than among those with controlled asthma. The same trend was seen regarding mental health, but only significantly so in treatment steps 1–3 (Figure 1).

**Subgroup analysis by treatment steps 1, 2, and 3**

The proportions of subjects with uncontrolled asthma were as follows; treatment step 1 (SABA or LABA without ICS) 24.0%, treatment step 2 (ICS as-needed) 20.2%, and treatment step 3 (ICS low dose with or without LABA) 27.2% \( (p = 0.453) \). The highest proportion of subjects with exacerbations (23.5%) were in treatment step 3, followed by step 2 (20.2%) and step 1 (10.4%), \( p = 0.018 \). No significant differences were found regarding any healthcare visits, ER-visits or physical or mental health, but subjects in treatment step 3 had significantly more physician follow-up visits than those in treatment steps 1 and 2 (Table 4).

**Discussion**

In this population-based adult asthma cohort, uncontrolled asthma occurred in all treatment steps, but was most common among those with treatment steps 4–5. Uncontrolled asthma was related to asthma exacerbations, healthcare utilization, and worse health status among all subjects. Although health status was associated with asthma control, it was not associated with the level of treatment (Figure 2). Regular follow-up visits to a physician or a nurse were uncommon. Our
Table 3. Asthma exacerbation, healthcare utilization and health status by subjects without asthma treatment, GINA treatment steps 1–3, and GINA treatment steps 4–5, comparing by asthma control.

<table>
<thead>
<tr>
<th></th>
<th>No treatment</th>
<th>Treatment steps 1–3</th>
<th>Treatment steps 4–5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled n=154 Uncontrolled n=17</td>
<td>Controlled n=277 Uncontrolled n=88</td>
<td>Controlled n=107 Uncontrolled n=71</td>
</tr>
<tr>
<td>Asthma exacerbation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma exacerbation last 12 months</td>
<td>15 (9.7)</td>
<td>4 (23.5)</td>
<td>0.086</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>38 (13.7)</td>
<td>28 (31.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency room visits last 12 months</td>
<td>7 (4.5)</td>
<td>2 (11.8)</td>
<td>0.206</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>16 (5.8)</td>
<td>17 (19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations last 12 months</td>
<td>4 (2.6)</td>
<td>0 (0.0)</td>
<td>0.501</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>2 (0.7)</td>
<td>3 (3.4)</td>
<td>0.059</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-ups visits, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 Physician follow-up visit per year</td>
<td>1 (0.6)</td>
<td>1 (5.9)</td>
<td>0.057</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>50 (18.1)</td>
<td>21 (23.9)</td>
<td>0.230</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 Nurse follow-up visit per year</td>
<td>1 (0.6)</td>
<td>1 (5.9)</td>
<td>0.057</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>27 (9.7)</td>
<td>14 (15.9)</td>
<td>0.111</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health status assessed with SF-8, m (sd)****</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component score</td>
<td>46.9 (9.3)</td>
<td>39.7 (8.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mental component score</td>
<td>51.0 (8.4)</td>
<td>48.0 (7.8)</td>
<td>0.168</td>
</tr>
<tr>
<td>Mental component score</td>
<td>50.8 (8.7)</td>
<td>46.7 (10.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mental component score</td>
<td>51.8 (8.4)</td>
<td>50.0 (10.0)</td>
<td>0.202</td>
</tr>
<tr>
<td>Mental component score</td>
<td>50.4 (10.0)</td>
<td>50.0 (10.0)</td>
<td>0.135</td>
</tr>
<tr>
<td>Mental component score</td>
<td>51.8 (8.4)</td>
<td>50.0 (10.0)</td>
<td>0.202</td>
</tr>
<tr>
<td>Mental component score</td>
<td>50.4 (10.0)</td>
<td>50.0 (10.0)</td>
<td>0.135</td>
</tr>
</tbody>
</table>

Notes. p values = Chi-square test, ANOVA or student’s T-test, as appropriate.  
sd = Standard deviation.  
*p values comparing controlled and uncontrolled asthma among those with no treatment, in treatment steps 1–3 and in treatment steps 4–5, respectively.  
**p values comparing those with uncontrolled asthma (no treatment, treatment steps 1–3 and treatment steps 4–5).  
***p values comparing those with controlled asthma (no treatment, treatment steps 1–3 and treatment steps 4–5).  
****n = 7 internal missing values.  
*p-Values < 0.05 are given in bold.
results also highlight sex-differences where a higher proportion of women than men had exacerbations, any healthcare visits, and regular follow-up visits. Further, women had a more impaired health status than men.

In our study, asthma treatment was self-reported and uncontrolled asthma was reported by 10% of the asthmatics without any treatment at all, by 25% of those in treatment steps 1–3, and by 40% in treatment steps 4–5. Further, in all treatment steps, subjects with uncontrolled asthma reported more asthma exacerbations, healthcare utilization, and worse physical health than those with controlled asthma. From a healthcare perspective, nonadherence to asthma guidelines is common and may cause an uncontrolled disease (21–23). Guidelines recommend the use of validated questionnaires to identify the level of asthma control (1,11), nevertheless only a minority of physicians use these questionnaires on a regular basis (21,24). In our study, we used the recommended ACT to identify uncontrolled asthma (13). A cut off of \( \leq 19 \) signals that a change in pharmacological treatment such as step-up treatment may be needed, and that the patient’s adherence and inhalation technique should be monitored on a regular basis (19). However, regular follow-up visits seem to be uncommon in the care
of subjects with asthma. In our study, only about 20–30% of asthmatics reported follow-up visit once per year. This result is consistent with another population-based study, also showing that follow-up visits at least once per year were associated with better adherence (25). This emphasizes the need of regular follow-up visits when asthma control, patient adherence, inhalation technique, and exacerbation history is assessed. Based on the result, healthcare professionals should identify pharmacological and nonpharmacological treatment that can improve the patients’ disease control. According to GINA 2019 (1,26), personalized asthma management implies both assessing, adjusting and reviewing response of treatment.

Already in 1999, the Asthma Insights and Reality in Europe (AIRE) study highlighted that asthma is dangerously under-treated in some patients (27). In our study, about one fourth did not use asthma treatment at all and some did only use SABA and/or LABA or ICS as-needed. This may indicate that these subjects have initiated step-down treatment by themselves, and it is well known that adherence to ICS is poor from a patient perspective (28). According to guideline recommendations (1,11), step-down of asthma treatment should be considered when asthma symptoms are controlled for 3 months and the patients have low risk for exacerbations. Importantly though, ICS treatment should not be withdrawn without careful considerations. A randomized controlled trial study has shown that low dose ICS maintenance treatment may increase asthma control and quality of life compared to the use of ICS/LABA as-needed among adults with mild asthma (29). In our population-based study, there were no significant differences in asthma control or physical and mental health respectively, when comparing subjects using low dose ICS maintenance with subjects using SABA and/or LABA and/or ICS only as-needed. These diverse results may be due to different health status questionnaires or differences with regard to the real life study design of our study compared to a controlled trial setting. Historically, physicians have had a slow acceptance rate of recommending daily use of ICS, due to concerns about serious negative side-effects of OCS (30), and it does appear that also asthma nurses still have concerns and thus often recommended as-needed use of ICS (31).

We have previously shown that adults with well-controlled asthma report similar health status as those without asthma (32). Others have shown that poor asthma control is related to worse health status, together with factors as advancing age and lower educational level (33). In this study, uncontrolled asthma was related to worse health status, but health status did not differ by treatment step. Thus, uncontrolled asthma seems to be associated to worse physical health in all treatment steps, while the trend was weaker regarding mental health. This suggests that asthma has less impact on mental health than on physical health. Similar trends have been presented in other population-based studies where the severity of asthma and chronic obstructive pulmonary disease (COPD) mainly seem to affect physical health, not mental health (34–36).

As shown by us and others (7,16,37,38), women have a more severe asthma than men. In our study, women used more pharmacological treatment, had more exacerbations and healthcare visits than men. Further, they had worse physical and mental health, and a higher proportion also had uncontrolled asthma, although not significantly so. Previous studies have also shown diverse results regarding asthma control, where some suggest that young women have a worse asthma control than men (10,39), while others display no differences concerning young adults with asthma (40), or among older women and men (39). As women in our study did not have worse lung function, more ER visits or hospitalization than men, our results are consistent with reports discussing that women have a different awareness of symptoms, thus taking actions earlier (38) and perhaps also a higher adherence to follow-up visits than men. In Sweden, also women with COPD seem to be more actively managed than men (41), but as in our study, it is unclear whether it is due to behavioral factors from the patient or health care perspective. Beside behavioral differences, gender differences in asthma are often discussed to be due to hormonal effects (7,37,39), and more research is still needed to determine whether these gender differences are due to biological, behavioral and/or social factors.

**Strengths and limitations**

The strengths of this study include the population-based design with a large sample size, giving a real life perspective on use of asthma treatment and asthma control in a well-described adult asthma cohort (16,18). The current study is based on individuals from this cohort that had current asthma in a long-term follow-up, why a healthy survivor bias cannot be ignored. Obesity, ischemic heart disease, low socioeconomic status, and older ages were associated with nonparticipation (18). Despite this, our cohort still
reflects the distribution of adult asthma in the general population in line with other studies in Sweden (5,25), indicating representativeness. Studies about adults with asthma are often based on subjects with a more severe disease recruited from healthcare, while population-based studies facilitates to also study subjects with a milder disease, those without treatment, and those not seeking healthcare on a regular basis.

A further strength is the use of validated instruments for assessment of asthma control and health status (13,20). ACT has been shown to be reliable, valid, and responsive to changes in asthma control also in patents not previously followed by healthcare professionals (19), why the questionnaire fits well in epidemiological studies. It may be a limitation that a disease specific asthma quality of life questionnaire not was used. However, the SF-8 was constructed to be a shorter generic health survey ideal to be used in large population-based surveys (20), also among subjects with asthma (40,42). Moreover, ACT and SF-8 takes the last four weeks into account, whereas the questions in the structured interview reflects the last 12 months. A further limitation of our study is that we have not assessed patient adherence to prescribed treatment, or inhalation technique, which is important before considering asthma severity. Therefore, instead to considering asthma severity, we classified our cohort into GINA treatment steps based on self-reported data about asthma treatment and not the prescribe dose (1,17).

**Conclusion**

This population-based study shows that uncontrolled asthma is common in all GINA treatment steps and is associated to worse health status, especially physical health. However, health status did not differ by treatment steps. Our result also highlights sex-differences; women with asthma seem to have more exacerbations, healthcare utilization, and a worse health status than men. Healthcare professionals should ask the patients systematically after what treatment regime they actually use, and adjust as appropriate. Regular follow-up visits to a physician or to a nurse are still uncommon. Follow-up visits may be one of the most important improvements in asthma care, with the aim to give patients a personalized asthma management plan according to guidelines recommendations.

**Acknowledgements**

Acknowledgements is given to the participants in the OLIN studies, Professor Bo Lundbäck and Professor Eva Rönmark. All in the research group are acknowledged for their excellent work, and especially our research nurses/assistants for data-collection; Britt-Marie Eklund, Ann-Christine Jonsson, Sigrid Sundberg and Viktor Strandkvist. Additional Acknowledgements are given to Sanofi, Sweden.

**Declaration of interest**

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

**Funding**

This work was supported by the Swedish Heart & Lung foundation under Grant number 20170509; The Swedish Research Council, a regional agreement between Umeå University and Västerbotten County Council (ALF); Norrbotten County Council; the Swedish Asthma-Allergy Foundation; and VISARE NORR Fund: Northern county councils Regional federation.

**Notes on contributor**

C.S. and H.B. designed the study and participated in data-collection. C.S., H.B., M.A., and K.W. were involved in data analysis and contributed in the writing of the manuscript.

**ORCID**

Caroline Stridsman http://orcid.org/0000-0001-6622-3838
Helena Backman http://orcid.org/0000-0002-0553-8067

**References**


