Time course of dementia following sepsis in German health claims data

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Abstract

Objective
We evaluated the short-, medium-, and long-term effects of sepsis on dementia incidence using German health claims data.

Methods
A total of 161,567 patients (65 years or older) were followed from 2004 to 2015 at quarterly intervals. Time since sepsis was categorized into 0 (the effective quarter of sepsis diagnosis), 1–8, and ≥9 quarters since the latest diagnosis of sepsis, taking into account admission to intensive care unit and controlling for delirium, surgery, age, sex, and comorbidities. Incident dementia was defined for all persons who did not have a validated dementia diagnosis in 2004 and 2005 and who received a first-time, valid diagnosis between 2006 and 2015.

Results
During the quarter of sepsis diagnosis, patients not admitted to intensive care had a 3.14-fold (95% CI 2.83–3.49) increased risk, and those with intensive care stay had a 2.22-fold (95% CI: 1.83–2.70) increased risk of receiving an incident dementia diagnosis compared with patients without sepsis. The impact of sepsis on incident dementia remained in the following 2 years, remitting only thereafter.

Conclusions
For sepsis survivors, medium-term dementia risk remains elevated, whereas long-term risk may reach the level of those without sepsis, even after controlling for delirium. These findings encourage identifying modifiable components of hospital and rehabilitation care.
Systemic inflammation caused by microbial infection, hereafter referred to as sepsis, compromises the function of peripheral organs, but also affects the brain. Immediate changes in cognition and behavior on sepsis have been collectively described as sickness behavior and functionally analyzed in rodent models and human patients with sepsis.\(^1\) There is little doubt that an acute inflammatory reaction of the brain leads to transient EEG changes, cognitive dysfunction, and memory deficits. Far less clear, however, are the mid- to long-term consequences of sepsis for brain function and integrity. Particularly, the risk of developing neurodegenerative disorders in the subsequent months and years requires careful examination.

Adult sepsis survivors were found to be impaired with regard to a whole scale of activities of daily living and also displayed an increase in mild to moderate cognitive deficits.\(^2\) Similarly, patients who were followed after intensive care unit (ICU) treatment for sepsis were found to have persistent slowing of EEG activity and memory deficits along with hippocampal volume reduction.\(^3\) Research has shown that diagnosis of sepsis, delirium, or critical illness in general and major surgeries are each often followed by an acute lowered cognitive ability, which may or may not be permanent.\(^4\)–\(^7\)

How these events overlap or interact is a Gordian knot. To further delineate postseptic cognitive changes in patients with sepsis, we used a health insurance data set, identifying incident diagnoses of dementia in the months and years after sepsis and controlling for specific important diseases and medical events.

**Methods**

**Data**

We analyzed dementia incidence using routine claims data of the largest German statutory health insurance, the Allgemeine Ortskrankenkasse (AOK). In Germany, 70 million people insured via statutory health insurance (about 84.7% of the total population); about one-third of these are insured through the AOK.\(^8\)

A random, 5-year age-stratified sample of insurance claimants born in or before 1939 and who had at least 1 day of insurance coverage by the AOK in the first quarter of 2004 was drawn by the Scientific Institute of the AOK (Wissenschaftliches Institut der AOK [WIdO]). Access to health claims data is strictly regulated by law to ensure privacy of claimants. Insurees were, therefore, anonymized such that individuals cannot be identified. A unique person ID was allocated to retrospectively track individuals from 2004 through 2015 at quarterly intervals to establish a longitudinal sample. Data are available on a quarterly basis because outpatient physicians settle services with the Associations of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen) quarterly. Because information on the organization of medical visits and the specific date of diagnoses were unavailable, we used quarters as the reference parameter regarding the definition of commencement and duration of specific events. The data included complete records of inpatient and outpatient treatment received. Excluding those with inconsistent or missing information regarding date of birth, date of death, or sex, and those with a diagnosis of either dementia or sepsis in the first 2 observation years (2004 or 2005) yielded a study sample of 161,567 participants. This was not a study with human participants requiring an internal review board evaluation. The WIdO legally granted data access.

**Definition of dementia**

We used coding of the *International Classification of Diseases, 10th Revision* (ICD-10 codes) to define dementia diagnosis: G30, G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05.1. We combined all ICD codes into 1 group named dementia. We applied an internal validation procedure to rule out false-positive diagnoses. First, both outpatient verified diagnoses and inpatient discharge or secondary diagnoses were selected. Second, if dementia was diagnosed during the same quarter in both the inpatient and outpatient settings or if at least 2 physicians (general practitioners, neurologists/psychiatrists, and other specialists) diagnosed dementia within the same quarter for a given individual, the diagnoses were considered valid. Dementia diagnoses were also confirmed by co-occurrence over time during the entire observation period. Last, dementia diagnoses were considered valid in the case of death within the quarter of dementia diagnosis, which precluded validation by a second diagnosis.\(^9\)–\(^10\)

Incident dementia was defined as the first occurrence of a valid dementia diagnosis between 2006 and 2015. Using a period of at least 2 years (2004 and 2005) without a valid dementia diagnosis avoids confusion between incident diagnoses and prevalent cases with a history of dementia.\(^9\)–\(^11\)

**Independent variables**

We explored whether time since the latest sepsis diagnosis, ICU stay, delirium diagnosis, and surgery during the period of observation 2006–2015 affected the risk of dementia by creating periods defined as 0 (the effective quarter of diagnosis/procedure), 1–8, and >9 quarters since the latest diagnosis or procedure, respectively. These time-varying variables allowed two issues to be accounted for. First, we were able to measure the time since the latest diagnosis or event. From a technical point of view, persons switch from 1 category to the next, depending on

**Glossary**

AOK = Allgemeine Ortskrankenkasse; HR = hazard ratio; ICD-10 = *International Classification of Diseases, 10th Revision*; ICU = intensive care unit; WIdO = Wissenschaftliches Institut der AOK.
the quarters since the latest event of interest. This approach also implicates that persons switch back again to the category indicating the effective quarter of the recurring event.

For descriptive analyses, we differentiated more intervals for time since the latest sepsis diagnosis, delirium, ICU stay, or surgeries: quarter 0, 1–2 quarters, 3–4 quarters, 2, 3, 4, 5, or ≥6 years (figure 1).

Sepsis was defined by ICD-10 code A41. Using both sepsis and admission to an ICU, we created a combined variable, which indicated whether a person had received a sepsis diagnosis in quarter 0, 1–8, or ≥9 quarters before, and we considered whether a person received intensive care in the quarter of the sepsis diagnosis. Deliria were defined by ICD-10 codes F05 (F05.1 excluded) and F06.

Surgeries were defined according to the classification of operational procedures (Operationen-und Prozedurenschlüssel),12 an adaptation of the former version of the current International Classification of Health Interventions.13 The complete code range of chapter 5 (Surgical procedures) was used, thus including a wide range from small to extensive surgeries.

We adjusted for comorbidities and for age and sex. The following diseases were coded according to ICD-10 classification: diabetes mellitus (E10–E14); hypertension (I10–I13 and I15); hypercholesterolemia (E78.0); cerebrovascular diseases (I60–I69, G45, G46, and H34.0); depression (F32, F33, and F341); and Parkinson disease (G20–G22). All of the diagnoses used in this study were billing-relevant outpatient-verified diagnoses or inpatient discharge or secondary diagnoses by physicians.

Statistical analysis
Methods of survival analysis were applied to explore the risk of incident dementia diagnosis. Calendar time of the observation period (2006–2015) was used to operationalize the underlying process time. Exploring the effect of sepsis diagnosis and ICU stay on dementia incidence was performed with the help of Cox models. We controlled for the occurrence of delirium diagnoses, surgeries, and for sex and time-varying information on age, cerebrovascular diseases, diabetes mellitus, hypertension, hypercholesterolemia, depression, and Parkinson disease. Individuals were followed to the time of incident dementia diagnosis, death, withdrawal from insurance, loss to follow-up, or December 31, 2015, whichever occurred first.

Furthermore, we explored mortality following a sepsis diagnosis by using Kaplan-Meier survival curves. A 1:1-matched case-control design was applied, in which each patient with sepsis diagnosis was matched to 1 patient without sepsis diagnosis with respect to age, sex, and index date. The index date was the date of the latest sepsis diagnosis before death or censoring. Patients with sepsis were further stratified according to those with and without intensive care stays during the quarter of sepsis diagnosis (N = 14,188; n_no sepsis = 7,094; n_sepsis, no ICU = 5,318; n_sepsis, ICU = 1,776).

Data availability
The WIdO has strict rules regarding data sharing because of the fact that health claims data are a sensible data source and have ethical restrictions imposed due to concerns regarding privacy. Anonymized data are available to all interested researchers on request. Interested individuals or an institution who wish to request access to the health claims data of the AOK, please contact the WIdO (webpage: wido.de/, email: wido@wido.bv.aok.de).

Results
The highest dementia incidence rate for each event group (latest sepsis diagnosis, ICU stay, delirium diagnosis, and

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Figure 1 Dementia incidence rates by time since the latest sepsis diagnosis, ICU stay, surgery, and delirium diagnosis (N = 161,567)

Source: Health claims data AOK 2004–2015; 95% CIs. AOK = Allgemeine Ortskrankenkasse; ICU = intensive care unit.
surgery) existed in the quarter (0) of the event itself. Incidence rates declined thereafter, but remained above the level of those without sepsis diagnosis, ICU stay, delirium diagnosis, or surgery, respectively (table 1, figure 1).

The incidence rate of dementia in the quarter of the sepsis diagnosis was disproportionally elevated among those aged 85 years and older (figure 2). This age gradient slightly attenuated over time since the latest sepsis diagnosis.

Table 2 presents the hazard ratios (HRs) for incident dementia diagnosis by time since sepsis diagnosis and distinguishes between patients who did or did not experience intensive care during the quarter of the sepsis diagnosis. It also

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Exposures</th>
<th>Incident dementia</th>
<th>Rate per 1,000 person-years</th>
<th>LCI</th>
<th>UCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since the latest sepsis diagnosis</td>
<td>No diagnosis</td>
<td>1,222,746.0</td>
<td>27,838</td>
<td>22.77</td>
<td>22.50</td>
<td>23.04</td>
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<tr>
<td></td>
<td>Quarter 0</td>
<td>2,072.0</td>
<td>477</td>
<td>230.21</td>
<td>210.45</td>
<td>251.83</td>
</tr>
<tr>
<td></td>
<td>1–8 quarters</td>
<td>6,024.0</td>
<td>328</td>
<td>54.45</td>
<td>48.86</td>
<td>60.67</td>
</tr>
<tr>
<td></td>
<td>≥9 quarters</td>
<td>5,856.5</td>
<td>208</td>
<td>35.52</td>
<td>31.00</td>
<td>40.69</td>
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<tr>
<td>Time since the latest ICU stay</td>
<td>No ICU stay</td>
<td>1,140,306.5</td>
<td>24,949</td>
<td>21.88</td>
<td>21.61</td>
<td>22.15</td>
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<tr>
<td></td>
<td>Quarter 0</td>
<td>6,425.5</td>
<td>1,048</td>
<td>163.10</td>
<td>153.52</td>
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<tr>
<td></td>
<td>1–8 quarters</td>
<td>34,476.8</td>
<td>1,310</td>
<td>38.00</td>
<td>35.99</td>
<td>40.11</td>
</tr>
<tr>
<td></td>
<td>≥9 quarters</td>
<td>55,489.8</td>
<td>1,544</td>
<td>27.82</td>
<td>26.47</td>
<td>29.25</td>
</tr>
<tr>
<td>Time since the latest surgery</td>
<td>No surgery</td>
<td>681,800.0</td>
<td>12,741</td>
<td>18.69</td>
<td>18.37</td>
<td>19.01</td>
</tr>
<tr>
<td></td>
<td>Quarter 0</td>
<td>32,173.9</td>
<td>2,895</td>
<td>89.98</td>
<td>86.76</td>
<td>93.32</td>
</tr>
<tr>
<td></td>
<td>1–8 quarters</td>
<td>196,827.0</td>
<td>5,261</td>
<td>26.73</td>
<td>26.02</td>
<td>27.46</td>
</tr>
<tr>
<td></td>
<td>≥9 quarters</td>
<td>325,897.6</td>
<td>7,954</td>
<td>24.41</td>
<td>23.88</td>
<td>24.95</td>
</tr>
<tr>
<td>Time since the latest delirium diagnosis</td>
<td>No diagnosis</td>
<td>1,207,336.0</td>
<td>24,710</td>
<td>20.47</td>
<td>20.21</td>
<td>20.72</td>
</tr>
<tr>
<td></td>
<td>Quarter 0</td>
<td>4,000.7</td>
<td>2,097</td>
<td>524.16</td>
<td>502.20</td>
<td>547.08</td>
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<td></td>
<td>1–8 quarters</td>
<td>13,556.5</td>
<td>1,364</td>
<td>100.62</td>
<td>95.42</td>
<td>106.10</td>
</tr>
<tr>
<td></td>
<td>≥9 quarters</td>
<td>11,805.3</td>
<td>680</td>
<td>57.60</td>
<td>53.43</td>
<td>62.10</td>
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<tr>
<td>Time since the latest sepsis diagnosis by ICU stay in quarter of sepsis diagnosis</td>
<td>No diagnosis, no ICU stay</td>
<td>1,216,886.5</td>
<td>26,924</td>
<td>22.13</td>
<td>21.86</td>
<td>22.39</td>
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<td></td>
<td>No diagnosis, ICU stay</td>
<td>5,859.5</td>
<td>914</td>
<td>155.99</td>
<td>146.19</td>
<td>166.43</td>
</tr>
<tr>
<td></td>
<td>Quarter 0, no ICU stay</td>
<td>1,679.8</td>
<td>372</td>
<td>221.45</td>
<td>200.05</td>
<td>245.14</td>
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<td></td>
<td>1–8 quarters, no ICU stay</td>
<td>4,880.8</td>
<td>256</td>
<td>52.45</td>
<td>46.40</td>
<td>59.29</td>
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<tr>
<td></td>
<td>9+ quarters no ICU stay</td>
<td>4,817.6</td>
<td>169</td>
<td>35.08</td>
<td>30.17</td>
<td>40.79</td>
</tr>
<tr>
<td></td>
<td>Quarter 0, ICU stay</td>
<td>392.2</td>
<td>105</td>
<td>267.74</td>
<td>221.13</td>
<td>324.18</td>
</tr>
<tr>
<td></td>
<td>1–8 quarters, ICU stay</td>
<td>1,143.2</td>
<td>72</td>
<td>62.98</td>
<td>49.99</td>
<td>79.35</td>
</tr>
<tr>
<td></td>
<td>9+ quarters, ICU stay</td>
<td>1,039.0</td>
<td>39</td>
<td>37.54</td>
<td>27.43</td>
<td>51.38</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,236,698.5</td>
<td>28,851</td>
<td>23.33</td>
<td>23.06</td>
<td>23.60</td>
</tr>
</tbody>
</table>

Abbreviations: + = in person-years; AOK = Allgemeine Ortskrankenkasse; ICU = intensive care unit; LCI = 95% lower CI; UCI = 95% upper CI.

Figure 2 Dementia incidence rates by time since sepsis diagnosis and age

![Graph showing dementia incidence rates by time since sepsis diagnosis](image)

Source: Health claims data AOK 2004-2015; 95% CIs. AOK = Allgemeine Ortskrankenkasse; ICU = intensive care unit.

shows the hazard ratios by time since delirium and surgery. All models were adjusted for comorbidities, age, and sex.

In model 1a, compared with cases without sepsis diagnosis, the hazard ratio of dementia was significantly increased during the quarter of sepsis diagnosis for both groups with (HR = 6.92, 95% CI: 5.72–8.39) and without ICU stay (HR = 6.06, 95% CI: 5.47–6.72). The effects remained significant, albeit at a lower level, at 1–8 quarters after sepsis (with ICU: HR = 2.17, 95% CI: 1.72–2.74; without ICU: HR = 1.60, 95% CI: 1.41–1.81). There appeared to be no long-term effects of sepsis diagnosis having taken place 9 or more quarters ago.

We find an altered pattern in model 2 after additionally adjusting for time since the latest delirium diagnosis and surgery. Compared with cases without sepsis diagnosis, the dementia risk in the immediate quarter of sepsis was now highest for persons without ICU stay (HR = 3.14, 95% CI: 2.83–3.49) and lower for those with ICU stay (HR = 2.22, 1.83–2.70). Medium-term effects continued to be significant (without ICU: HR = 1.36, 95% CI: 1.20–1.54; with ICU: HR = 1.55, 95% CI: 1.23–1.96), whereas long-term effects are still nonexistent.

Model 1b explores the effect of delirium on dementia incidence, which was highest in the immediate quarter of the delirium diagnosis (HR = 10.81, 95% CI: 10.33–11.32) but also remained significant, albeit at a lower level, in the medium (HR = 2.33, 95% CI: 2.20–2.46) and longer term (HR = 1.43, 95% CI: 1.32–1.54). Controlling for sepsis, ICU stay, and surgery, the effect of delirium was attenuated but remained significant, with the highest HR in quarter 0 (HR = 7.36, 95% CI: 7.01–7.73) and dropping off thereafter (model 2).

Model 1c shows the effect of surgeries on the risk of dementia. Similar to sepsis and delirium, the hazard ratio of dementia was significantly increased during the quarter of surgery (quarter 0: HR = 3.66, 95% CI: 3.52–3.81) and 1–8 quarters after surgery (HR = 1.13, 95% CI: 1.10–1.17). Effects slightly attenuated in model 2.

Calculating the number needed to harm from a model that distinguishes individuals who never had a sepsis from those who ever had one, we arrived at a figure of 51 for the median follow-up time of 7.625 years (table e-1, links.lww.com/NXI/A350). This implies that 1 of 51 individuals having ever had sepsis receives an incident dementia diagnosis.

To compare the mortality patterns between patients with and without intensive care in the quarter of the sepsis diagnosis, we used Kaplan-Meier survival curves (figure 3). Compared with patients without ICU stay, the Kaplan-Meier-curve demonstrated a stark survival disadvantage of those with ICU stay during the quarter of the sepsis diagnosis. The parallel trajectory of the survival curves in the following quarters, however, suggested no long-term effect of ICU stay on mortality.

We performed sensitivity analyses using a subsample without patients with a delirium diagnosis and a subsample without patients with a delirium diagnosis, surgery, or ICU treatment during the observation period to examine the robustness of the results. We yielded consistent results for regression models and Kaplan-Meier survival analysis (table e-2 and figure e-1, links.lww.com/NXI/A350).

Discussion

Next to acute and negative symptoms of sepsis on cognition and behavior, persistent cognitive deficits have been demonstrated, and an increased risk of developing neurodegenerative disorders has been postulated. Using a large sample of claims data obtained from the largest German statutory health insurance, we showed that as expected, delirium most frequently preceded with diagnosis of dementia. Next followed an independent effect of a prior diagnosis of sepsis, then a prior occurrence of an ICU stay and a previous surgery. For all of these clinical events, the incidence of dementia diagnosis was highest in the quarter during which the respective clinical event occurred. Thereafter incidence declined, but continued to persist at a raised level up to 2 years. This may suggest that the described clinical events all represent risk factors for a relatively rapid cognitive decline, even reaching the level of dementia within the first quarter.

A possible confounding factor could have been the higher medical attention that patients having these conditions received during hospitalization, and thus, previously unrecognized dementia cases may have been identified for the first time. Alternatively, clinical events such as perturbation of cerebral homeostasis during sepsis, delirium, procedures during ICU, or surgery may have accelerated clinically silent cases of predementia syndromes, moreover, because age represents the strongest risk factor for the development of dementia and all included patients were aged 65 years or
older. This is supported by our finding that the immediate effect of sepsis on dementia diagnosis was largest among those aged 85 years and older. Last, documented delirium does not cover all cases of delirium, which actually occurred. Hence, the effect of delirium, which was coded, was higher than that of sepsis, which is not equivalent to the effect of delirium per se. Further, the observation period of 2 years without a diagnosis of either dementia or sepsis does not exclude the possibility that a case of sepsis occurred prior to 2004. Nor does it exclude a given claimant having had experienced previous ICU stays or surgical procedures.

Precise pathologic mechanisms could not be identified by our data set due to the diversity of microbial pathogens inducing sepsis, the heterogeneity of pathogenetic mechanisms underlying delirium,15 the different interventions during an ICU stay, or the different surgical procedures. Despite this, all 4 clinical events were subsequently associated with the increased incidence of dementia either concurrently or thereafter. This is congruous with previous studies showing increased incidence of cognitive decline and dementia after sepsis,2,16,17 delirium,18–20 hospitalization for critical illness,4,5,21 and cardiac and noncardiac surgery.22,23 Possible mechanisms that may contribute to the sepsis-induced neurocognitive deterioration may include compromised microglial clearance function and subsequent accumulation of cerebral beta-amyloid,24 inflammatory changes at the synapse level25 or increased susceptibility to excitotoxic events after exposure to bacterial lipopolysaccharide.26 It is important to note that pathogenetic mechanisms have mostly been identified using rodent models, which in the case of sepsis share only a minor number of molecular signaling mechanisms with men.27 Thus, the underlying pathologic processes need to be further explored in particular in humanized models or the actual human cases itself. Of note, the incidence of dementia diagnoses following the described clinical events progressively lessened during the subsequent quarters, yet remained significantly greater than that of the respective case controls up to 2 years after the event. For delirium, the effect extended even beyond this period.

### Table 2

Cox proportional hazard models for the complete sample with outcome incidence of dementia diagnosis

<table>
<thead>
<tr>
<th>Time since the latest sepsis diagnosis by ICU stay in quarter 0</th>
<th>Model 1a–c</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>p Value</td>
<td>LCI</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>No diagnosis, no ICU (RG)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No diagnosis, ICU</td>
<td>4.70</td>
<td>0.000</td>
</tr>
<tr>
<td>Quarter 0, no ICU</td>
<td>6.06</td>
<td>0.000</td>
</tr>
<tr>
<td>1–8 quarters, no ICU</td>
<td>1.60</td>
<td>0.000</td>
</tr>
<tr>
<td>9+ quarters, no ICU</td>
<td>1.14</td>
<td>0.101</td>
</tr>
<tr>
<td>Quarter 0, ICU</td>
<td>6.92</td>
<td>0.000</td>
</tr>
<tr>
<td>1–8 quarters, ICU</td>
<td>2.17</td>
<td>0.000</td>
</tr>
<tr>
<td>9+ quarters, ICU</td>
<td>1.18</td>
<td>0.296</td>
</tr>
</tbody>
</table>

Time since the latest delirium diagnosis

<table>
<thead>
<tr>
<th>No diagnosis (RG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.81</td>
</tr>
<tr>
<td>Quarter 0</td>
</tr>
<tr>
<td>2.33</td>
</tr>
<tr>
<td>9+ quarters</td>
</tr>
<tr>
<td>1.43</td>
</tr>
</tbody>
</table>

Time since the latest surgery

<table>
<thead>
<tr>
<th>No surgery (RG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.66</td>
</tr>
<tr>
<td>Quarter 0</td>
</tr>
<tr>
<td>1.13</td>
</tr>
<tr>
<td>9+ quarters</td>
</tr>
<tr>
<td>1.03</td>
</tr>
</tbody>
</table>

Abbreviations: AOK = Allgemeine Ortskrankenkasse; HR = hazard ratio; ICU = intensive care unit; LCI = 95% lower CI; RG = reference group; UCI = 95% upper CI.

Source: Health claims data AOK 2004–2015; N = 161,567; all models adjusted for age, sex, cerebrovascular diseases, hypertension, diabetes, hypercholesterolemia, depression, and Parkinson disease; models 1a–c show the gross effect of the variable of interest unadjusted for the other information but adjusted for age, sex, cerebrovascular diseases, hypertension, diabetes, hypercholesterolemia, depression, and Parkinson disease; model 2 shows the joint effects of sepsis, ICU stay, delirium, and surgery.
The comparison of different age clusters (65–74, 75–84, and 85+ years) revealed that dementia incidence after sepsis increased by age and that the oldest cluster was at highest risk of incidental dementia after sepsis, possibly indicating a contributing factor of immune senescence or reduced compensatory mechanisms of the brain to cope with the sepsis-caused challenge. Nevertheless, it seems important to note that the risk of developing dementia and, in particular, Alzheimer disease follows a similar age-dependent slope. When considering the decrease of incident dementia after the quarter of the respective clinical event, one may have expected a longer lasting effect of sepsis on the risk of developing dementia. One reason why sepsis may not show a more obvious effect on the incidence of dementia in the subsequent years may be the increased mortality of patients after initially surviving sepsis, which is in line with earlier epidemiologic studies of sepsis-related mortality. Here, cases of hospitalization in an ICU showed increased mortality as compared to sepsis cases, which had not required intensive care. One underlying and frequent reason for ICU admission during sepsis is the occurrence of a multiorgan failure, which may reflect the severity of the infection, the frailty of the respective individual, and, certainly, a higher risk of cerebral involvement. The results may indicate a selection effect, with less cognitive-impaired and less frail individuals being healthy enough to survive the rigors of intensive care. Either way it is remarkable that sepsis increases mortality immediately in its aftermath but has no medium- and long-term consequences on survival.

One major methodological problem is to cleanly separate the effects of delirium, sepsis, and underlying acute or chronic diseases. However, the effect of sepsis on dementia risk in our data was independent of other critical events, age, sex, or comorbidities. In sensitivity analyses excluding patients with a delirium diagnosis, as a strong driver for dementia risk, we yielded consistent results for sepsis. Another problem is that we cannot differentiate between primary degenerative, progressive, and irreversible cognitive decline and potentially reversible dementia of secondary origin. The latter may be caused by physical diseases or injuries. For example, distinguishing delirium from dementia can be difficult. If such reversible dementia is assigned to one of the dementia diagnoses included in our study and persists over a longer period, our validation procedure may define these cases as valid dementia cases. Using the subsample without patients with delirium diagnosis, surgery or ICU treatment may partly exclude cases with potentially reversible dementia due to these critical events. Again, we yielded consistent results for sepsis.

The primary objectives of administrative health claims data are cost reimbursement and calculation, with implications for secondary data analyses. Not every diagnosis is relevant for the purposes of cost calculation. Thus, a patient’s cognitive impairment or mild dementia might not be documented if no further treatment is given. The incidence of dementia will certainly be biased to higher ages, when the symptoms of the disease become more obvious. We thus cannot explore premorbid cognitive data as long as there is no diagnosis. Hence, it is difficult to disentangle whether such patients may in fact have had preexisting cognitive impairments or generally lower cognitive abilities before the major event, potentially even leading to a higher risk of admission to ICU or diagnoses such as sepsis or delirium. Our results may partly reflect such reverse causality. Preliminary analyses with sepsis diagnosis as the dependent variable revealed that ever experiencing a dementia diagnosis during the observation period is associated with an increased risk of incident sepsis diagnosis (results available on request), indicating such...
bidirectional relationships. Delirium is known to be under-coded in administrative data using ICD, ninth edition or ICD-10 criteria compared with data using, e.g., Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Delirium diagnoses, particularly in severe cases, are most often made in the inpatient setting where we are not able to define the specific type of physician who made the diagnosis. In general, such a diagnostic code is made either by a neurologist or psychiatrist. Furthermore, we are not able to define the severity of sepsis. Health claims data do not include clinical parameters, and clinical sepsis codes (R65.0! for sepsis and R65.1! for severe sepsis in 2005; R57.2 for septic shock in 2010) were introduced later and may not have been used consistently over time. In our study, we used ICD code A41, which may be associated with an underestimation of sepsis cases, but with a high positive predictive value.

We analyzed a nationwide population-based data set with a large sample size that allowed investigating the relationship between sepsis and dementia. The analysis of health claims data avoids potential biases that often occur in population-based surveys. There is no bias arising from response behavior or self-selection, selection by the health care provider, or the study design. In particular, community dwelling and people living in nursing homes are included, with the latter usually missing in surveys. All of the data were legally made available in anonymous form, thereby eschewing any selection bias due to active volunteerism. In addition, medical diagnoses were documented, preventing recall bias by individual participants, and were validated, avoiding use of false-positive diagnoses.

Our observational study showed that for up to 2 years after sepsis, incidents of dementia doubled and even tripled compared with those without sepsis, after accounting for other clinical events, such as delirium. Hence, incident dementia may be precipitated by or perhaps even induced by sepsis, in addition to or in combination with other clinical events such as delirium, surgery, and/or intensive care stay. To our knowledge, this independent effect has not been shown for sepsis diagnosis until now. Further research using primary data analysis will need to consider factors ameliorating or rescuing patients from cognitive decline and dementia following these events. Focus should rest on medical therapies and interventions, premorbid cognitive ability, including cognitive reserve, psychiatric illness, physical rehabilitation and after care, and potential confluences of causal factors sepsis and delirium and neurodegeneration.

Dementia diagnoses in medical claims data are neither specific nor standardized, and a claims-based definition of dementia and other diagnoses is not the same as prospective clinical assessment. However, the prevalence and incidence based on AOK claims data fit well with other national and international studies. Furthermore, using formal medical diagnoses prevents recall bias by the patient. Health claims data do not provide lifestyle and medical information, such as intensity of former or current tobacco use, dietary habits, or body mass index, which could potentially affect the association between sepsis and dementia.

We therefore used an overall indicator for dementia.

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Disclosure
T. Fritze, G. Doblhammer, and C.N. Widmann report no disclosure relevant to the manuscript. M. Heneka acts as an advisory board member of IFM Therapeutics, Alector, Tiaki and Vigil Neuroscience. Go to Neurology.org/NN for full disclosures.

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<table>
<thead>
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<tbody>
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<td>Designed and conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content</td>
</tr>
</tbody>
</table>

Appendix
### References


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