Opioid prescribing patterns among medical providers in the United States, 2003-17
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Study question How are opioid prescriptions distributed across medical providers (eg, physician, nurse practitioner) in the US?

Methods This retrospective, observational study identified all opioid prescriptions from a national private insurer. Opioid prescriptions were converted to standardised opioid doses to account for differences in potency. The total dose and number of opioid prescriptions were calculated for each year and provider. Providers were ranked and the top 1% was compared with the middle 1%. Additionally, the proportion of overlap in adjacent years of the top 1% of providers was assessed.

Study answer and limitations In 2017, the top 1% of providers accounted for 49% of all opioid doses and 27% of all opioid prescriptions. In absolute terms, the top 1% of providers prescribed an average of 748,000 opioid doses—nearly 1000 times more than the middle 1%. More than half of all providers in the top 1% in any year were also in the top 1% in adjacent years. These data are from a single national insurer and may not be generalisable to the whole of the US. Importantly, the clinical appropriateness of prescriptions could not be assessed.

What this study adds This study showed that about 1% of providers account for nearly half of all opioid doses and one quarter of all opioid prescriptions in the US using a demographically representative sample.

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Soy intake and health

ORIGINAL RESEARCH Prospective cohort study

Association of soy and fermented soy product intake with total and cause specific mortality

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Study question What is the association between all and specific types of soy products and all cause and cause specific mortality?

Methods The study sample comprised 92 915 participants (42 750 men and 50 165 women) aged 45 to 74 years in Japan, a country with a high consumption of processed soy products. The association between intake of total soy products, fermented soy products (natto and miso), non-fermented soy products, and tofu and all cause and cause specific mortality (cancer, total cardiovascular disease, heart disease, cerebrovascular disease, respiratory disease, and injury) were examined. Participants were divided into fifths of intake for each of these products.

Study answer and limitations During 14.8 years of follow-up, 13 303 deaths were identified. Compared with the lowest fifth of soy product intake, the hazard ratios in the highest fifth were 0.98 (95% confidence interval 0.91 to 1.06, P trend=0.43) in men and 0.98 (0.89 to 1.08, P trend=0.46) in women. Intake of fermented soy products was inversely associated with all cause mortality in both men and women (highest versus lowest fifth: 0.90 (0.83 to 0.97), P trend=0.05 in men, and 0.89 (0.80 to 0.98), P trend=0.01 in women). Natto showed significant and inverse associations with total cardiovascular disease related mortality in men and women. A limitation of this study is that unmeasured confounding might attenuate the association.

What this study adds The findings of this study suggest that a higher intake of fermented soy is associated with a lower risk of mortality. A significant association between intake of total soy products and all cause mortality was not, however, observed.

Funding, competing interests, and data sharing This study was supported by National Cancer Center research and development fund (since 2011) and a grant-in-aid for cancer research from the Japanese Ministry of Health, Labour, and Welfare (1989-2010). The authors have no conflict of interests to declare. For information on how to submit an application for gaining access to Japan Public Health Centre-based Prospective Study data, follow the instructions at http://epi.ncc.go.jp/en/phc/805/8155.html.

COMMENTARY Japanese study links fermented soy to lower mortality

Soy is rich in protein, fibre, and unsaturated fat, as well as isoflavones. Some components of soy have been associated with beneficial effects on metabolic disorders such as cholesterolaemia and obesity. Recently, soy has been increasing in popularity not only among vegetarians but also in omnivores in Western countries, although Asian populations have typically eaten soy since ancient times.

In Asian countries, especially Japan, several types of soy products are widely consumed, such as tofu (soybean curd), natto (soybean fermented with Bacillus subtilis), and miso (soybean fermented with Aspergillus oryzae). It is, however, still unclear whether different soy products, especially fermented soy products, are associated with specific health effects.

Katagiri and colleagues examined associations between intake of soy products and total and cause specific mortality in 42 750 men and 50 165 women aged 45-74 in a prospective study based in 11 of Japan’s public health centre areas. During the 14.8 years of follow-up, the authors found that a higher intake of fermented soy (natto and miso) was associated with a significantly lower risk of all cause mortality. Further, men and women who ate natto had a lower risk of cardiovascular mortality than those who did not eat natto.

High salt content Fermented soy products are not usually consumed alone. For example, miso, one of the major fermented soy products, is a seasoning containing 12.4 g of salt per 100 g of miso (rice-koji miso, a light yellow type). Recently, many food manufacturers in Japan have been developing salt reduced foods including miso, informed by lessons from the UK’s salt reduction programme. However, salt content in miso was higher in 1995 and 1998 when these authors conducted their dietary surveys. Because the authors did not adjust for salt intake, which is a strong risk factor for non-communicable diseases, mortality, and morbidity, the association between higher miso intake and lower mortality might be confounded, and possibly underestimated. Future studies are needed to evaluate the health effects of more recent salt reduced miso products.

Taste for natto is highly variable, even in Japan, because of its distinct smell.
Risks of all cause mortality according to fifths of total soy and fermented soy product intake in Japanese men and women

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men (n=42 750)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Women (n=50 165)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total soy products*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intake (g/day)</td>
<td>&lt;53.2</td>
<td>53.2-79.2</td>
<td>79.2-104.6</td>
<td>104.6-141.3</td>
<td>&gt;141.3</td>
<td>&lt;51.6</td>
<td>51.6-75.3</td>
<td>75.3-99.7</td>
<td>99.7-135.9</td>
<td>&gt;135.9</td>
</tr>
<tr>
<td>No of deaths</td>
<td>1531</td>
<td>1593</td>
<td>1626</td>
<td>1676</td>
<td>1944</td>
<td>942</td>
<td>958</td>
<td>917</td>
<td>977</td>
<td>1139</td>
</tr>
<tr>
<td>Adjusted model†</td>
<td>1.00</td>
<td>0.96</td>
<td>0.94</td>
<td>0.91</td>
<td>0.98</td>
<td>0.43</td>
<td>1.00</td>
<td>1.01</td>
<td>0.95</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>(0.89 to 1.03)</td>
<td>(0.87 to 0.98)</td>
<td>(0.84 to 0.98)</td>
<td>(0.91 to 1.06)</td>
<td>(0.91 to 0.98)</td>
<td></td>
<td>(0.87 to 0.98)</td>
<td>(0.92 to 1.11)</td>
<td>(0.92 to 1.04)</td>
<td>(0.87 to 0.98)</td>
</tr>
</tbody>
</table>

Fermented soy products‡:

| Intake (g/day)             | <13.4          | 13.4-24.1       | 24.1-35.3       | 35.3-50.2       | >50.2           | <12.5            | 12.5-22.2       | 22.2-32.9       | 32.9-46.6       | >46.6           |
| No of deaths               | 1657           | 1530            | 1600            | 1763            | 1820            | 1033             | 955             | 925             | 963             | 1057            |
| Adjusted model†            | 1.00           | 0.92            | 0.91            | 0.95            | 0.90            | 0.05             | 1.00           | 0.95            | 0.91            | 0.90            |
|                           | (0.85 to 0.98) | (0.85 to 0.98)  | (0.88 to 0.98)  | (0.88 to 0.93)  | (0.83 to 0.97)  |                  | (0.87 to 0.88)  | (0.83 to 0.88)  | (0.81 to 0.88)  | (0.80 to 0.80)  |

*Sum of natto, miso, three kinds of tofu (tofu, yushidofu, and koyadofu), fried tofu (abura-age), and soy milk.
†Adjusted for age, geographical area, smoking, frequency of alcohol intake, body mass index, sports or physical exercise, history of diabetes or taking drugs for diabetes, taking antihypertensives, health check- up, total energy intake, and intake of green tea, coffee, fish, meat, fruit, and vegetables.
‡Sum of natto and miso.

Some countries already include soy and fermented soy products in their dietary guidelines

and stickiness, and the National Health and Nutrition Survey reported a median intake of 0 g for both men and women. In Katagiri and colleagues’ study, women who ate even small amounts of natto had a lower risk of total cardiovascular mortality than women who did not eat it.

More research is needed to clarify the causal effects of natto on health outcomes. Simultaneously, perhaps efforts should be made to develop a fermented soy food that is more acceptable to the public palate. Tempeh (soybean fermented with Rhizopus) was originally developed in Indonesia, and it is recommended in Finland as an alternative protein source to meat. However, the health effect of tempeh remains unclear.

Increasing evidence has suggested that fermented soy products are associated with health benefits. Whether people eat those products depends on their food culture, but some countries already include soy and fermented soy products in their dietary guidelines. Further studies are still required, however, to refine our understanding of the health effects of fermented soy, and perhaps to inform the development of healthier and more palatable products. These efforts should be collaborative, including not only researchers but also policy makers and the food industry.

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Maternal smoking during pregnancy and fractures in offspring

Brand JS, Hiyoshi A, Cao Y, Lawlor DA, Cnattingius S, Montgomery S

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Study question Does maternal smoking during pregnancy have an effect on the risk of fractures in offspring from early infancy to early adulthood?

Methods This was a national register based cohort study including 1,680,307 individuals born in Sweden between 1983 and 2000 to women who smoked (n=377,367) and did not smoke (n=1,302,940) in early pregnancy. All participants were followed-up until 31 December 2014. Rates of fractures (recorded in Swedish national registers) from birth to 32 years of age were compared in those exposed and unexposed to maternal smoking during pregnancy. Whole cohort and within-sibship analyses were performed to control for confounding by measured and unmeasured shared familial characteristics.

Study answer and limitations Offspring exposed to maternal smoking had an increased rate of fractures before the age of 1 year and between the ages of 5 and 32 years compared with those unexposed. Evidence of a dose dependent and within-sibship association, however, was only found for fractures before the age of 1 year. Study limitations include measurement error from maternal self-report of smoking in early pregnancy only, which could have resulted in an underestimation of the associations observed.

What this study adds This study suggests that intrauterine exposure to smoking is associated with an increased risk of fractures in the first year of life but does not have a long lasting biological influence on risk later in childhood and up to early adulthood.

Maternal smoking during pregnancy and risk of fractures in offspring by attained age. Hazard ratios (95% confidence intervals) for fractures comparing offspring exposed to maternal smoking during pregnancy (any, 1-9 cigarettes/day, ≥10 cigarettes/day) with those unexposed (reference group).

Model 1: whole cohort analysis adjusted for birth year; model 2: whole cohort analysis adjusted for birth year, sex of offspring, maternal age, parity, height, body mass index, parental education, occupation, and marital status; and model 3: within-sibship analysis including all model 2 covariates except for maternal height.

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