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The effect of gas cooking on bronchial hyperresponsiveness and the role of immunoglobulin E

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The effect of gas cooking on bronchial hyperresponsiveness and the role of immunoglobulin E. M. Kerkhoft, J.G.R.. de Monchy, B. Rijcken, J.P. Schouten. ©ERS Journals Ltd 1999.
ABSTRACT: Some studies have shown an association between gas cooking and respiratory symptoms. This study investigated whether gas cooking affects bronchial responsiveness and whether particular subjects are more sensitive to this effect.

Multiple linear regression analysis was performed with the dose-response slope (Percentage fall in forced expiratory volume in one second (FEV_1) divided by total dose of methacholine given) as the dependent variable in 1,921 subjects from a random sample of the Dutch population, aged 20–70 yrs. Whether the association was different according to sex, age, total immunoglobulin (Ig)E, specific IgE to inhalant allergens or smoking habits was tested by including interaction terms into the regression model.

Subjects who used gas for cooking had a higher prevalence of bronchial hyperresponsiveness (provocative dose causing a 20% fall in FEV_1 (PD_{20}) $\leq$2 mg) than those who used electricity (21% *versus* 14%) and this was dependent on the presence of atopy. Especially subjects with total IgE levels in the highest quartile had a significantly higher dose-response slope when using gas for cooking. This was independent of the presence of specific IgE to inhalant allergens.

These results show increased bronchial responsiveness with gas cooking, which was only found in subjects with high total immunoglobulin E levels. This suggests that atopic subjects are sensitive to adverse effects of gas cooking on respiratory health.
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Several epidemiological investigations have been carried out to assess the relationship between exposure to combustion products from gas cooking appliances and respiratory health [1–11]. Those studies have focused on respiratory symptoms and the level of pulmonary function. The reported effects of gas cooking are small and not consistent. Recently, JARVIS *et al.* [11] examined the association of respiratory symptoms and lung function with the use of gas for cooking using data from 14 countries collected as part of the European Community Health Survey. The overall meta-analysis showed a positive association between gas cooking and asthma-like symptoms in females. However, this was not consistently observed in all populations and not confirmed by objective markers of lung function. The heterogeneity of the association between gas cooking and symptoms may be explained by the presence of some factor that modifies the association.

NO_2 is probably the most important combustion product of gas. NO_2 is able to penetrate to the terminal bronchiole and the proximal alveolus. At high concentrations it unquestionably causes lung damage [12]. In houses with gas cooking appliances, higher mean levels of NO_2 were found, not only in the kitchen but also in bedrooms [13] and living rooms [14]. Some epidemiological studies have reported increasing prevalences of respiratory diseases and lower lung function parameters with increasing exposure to NO_2 [2, 15, 16]. The effect of inhalation of NO_2 has also been studied by experimental exposure in both normal subjects and susceptible patients [17]. Studies examining responses of healthy volunteers to acute exposure to NO_2 have generally failed to show alterations in lung function [17]. However, some studies have suggested that asthmatics are particularly sensitive to NO_2 by showing an enhanced airway response to inhaled allergen after exposure to NO_2 [18–21].

A possible intermediate between exposure and respiratory symptoms or lung function may be bronchial hyperresponsiveness (BHR). Subjects with BHR have more frequent respiratory symptoms and reduced lung function [22, 23]. It is unknown, however, whether BHR is more frequently present among subjects who use gas for cooking compared to electricity. Experimental exposure to NO_2 in animals was shown to induce BHR [24, 25].

In the current study, the authors investigated whether subjects exposed to combustion products of domestic gas appliances have an increased bronchial responsiveness compared to subjects from households with electric cookers. They also investigated whether sex, age, total immunoglobulin (Ig)E levels or specific IgE to inhalant allergens modify the effects of indoor air pollution.

Materials and methods

Subjects

In the first stage of the Dutch part of the European Community Respiratory Health Survey (ECRHS) [26, 27]

a postal screening-questionnaire was sent to all the subjects from a random sample of 23,976 subjects from the general population of three areas in the Netherlands (the city of Groningen and the towns of Roosendaal and Geleen both with adjacent rural communities). In the second stage of the study a second random sample, stratified by sex and 10-yrs age groups of 4,522 subjects, aged 20–70 yrs, was drawn out of the 23,976 subjects. All 4,522 subjects were invited to an examination of whom 2,711 subjects responded. The examination consisted of the administration of a questionnaire on respiratory symptoms and risk factors by a trained interviewer, lung function testing, measurement of bronchial responsiveness by methacholine provocation, skin-prick tests with nine inhalant allergens and venous blood collection for IgE and haematology.

Complete data consisting of questionnaire, bronchial responsiveness, total IgE and specific IgE to *Dermatophagoides pteronyssinus*, cat, timothy grass, birch and *Cladosporium herbarum* were obtained from 1,924 subjects in the period February 1992 to February 1993.

Data analysis

Prevalences of BHR, respiratory symptoms, current smoking and positive specific IgE to inhalant allergens were compared between subjects who used gas and subjects who used electricity for cooking by Chi-squared tests. To investigate whether sex, age, total IgE levels, specific IgE to inhalant allergens or current smoking modify the association between type of cooking and bronchial responsiveness, prevalences of BHR by type of cooking were evaluated after stratification by these variables.

To study the relationship between type of cooking and bronchial responsiveness with simultaneous adjustment for other explanatory factors, multiple linear regression analysis was performed with the logarithm of the dose-response slope as the dependent variable. The dose-response slope (range -2.99–4142.87) was calculated for each subject as percentage decline in forced expiratory volume in one second (FEV_1) from post-saline value at the last dose of methacholine divided by the cumulative dose of methacholine given. Before it was expressed on a logarithmic scale $3\%\cdot mg\ methacholine^{-1}$ was added to eliminate negative and zero values. Three subjects who had a >6% increase in FEV_1 after a dose of 2 mg methacholine were excluded from the linear regression analysis. Tests for interaction were used to examine whether the effect of gas cooking varied with total IgE, specific IgE, sex, age, and current smoking. To study whether characteristics of the home were confounding the relationship of gas cooking with bronchial responsiveness, adjustment was made for age of the home, type of heating, home dampness or water damage, and several characteristics of furnishing. The effect of adjustment for the variable "age at which full time education was completed" on the relationship between gas cooking and bronchial responsiveness was studied, since it may indicate socioeconomic status.

Methods of measurement

All measurements were performed according to the protocols of the European Community Respiratory Health Survey [27] and the detailed methods have been published previously [26]. Bronchial responsiveness was measured by methacholine inhalation using a Mefar dosimeter (Mefar, Brescia, Italy). Subjects who were not able to perform successful FEV_1 and forced vital capacity (FVC) manoeuvres or had an FEV_1 <70% of the mean predicted value or an FEV_1 <1.5 L were excluded from methacholine challenge. Other exclusion criteria were a heart attack in the last 3 months, any heart disease for which medication was used, epilepsy for which medication was used, pregnancy, breast feeding or the use of a β-blocker.

Subjects were advised to avoid smoking for 1 h, using a β_2-agonist or anticholinergic inhaler for 4 h or oral medication (β_2-agonist, theophylline or antimuscarinic) for 8 h before the test. In symptomatic subjects, methacholine challenge was performed according to a long protocol of doubling the cumulative dose of methacholine after a starting dose of 7.8 μg up to a cumulative dose of 2 mg. In asymptomatic subjects a short protocol was followed in which doses were quadrupled after a starting dose of 15.6 μg. The challenge was stopped if there was a 20% fall in FEV_1 from the control value in the best of two technically satisfactory manoeuvres performed after each, inhalation. Subjects who had a decline in FEV_1 of 20% or more after 2 mg or less methacholine were classified as BHR. Total and specific IgE were measured using the Pharmacia CAP System (Pharmacia diagnostics AB, Uppsala, Sweden). The CAP was performed in the laboratories of Pharmacia diagnostics AB. The assay is calibrated against the World Health Organisation (WHO) Standard for IgE, with a range of 0.35–100 $kU\cdot L^{-1}$ for specific IgE and 2–2000 $kU\cdot L^{-1}$ for total IgE. A high total IgE was defined as a total IgE level in the highest quartile according to sex (>105 $kU\cdot L^{-1}$ for males and 68 $kU\cdot L^{-1}$ for females). Specific IgE was measured to five common inhalant allergens: house dust mite *D. pteronyssinus*), cat, timothy grass, birch and *C. herbarum*. Specific IgE tests were considered positive at levels of 0.35 $kU\cdot L^{-1}$ or higher class (≥class 1)

Data on symptoms, smoking and home characteristics were obtained by the ECRHS questionnaire [27].

A smoker was defined as a subject who had smoked at least 20 packs of cigarettes or 360 g of tobacco in a lifetime, or at least one cigarette per day or one cigar a week for 1 yr; ex-smokers had stopped smoking at least 1 month before the survey. Since there was no difference in the relationship of bronchial responsiveness with the type of cooking between exsmokers and subjects who had never smoked, the presence or absence of current smoking was used in all of the analyses.

The statistical analyses were performed using Chi-squared tests and multiple linear regression analysis. p-values <0.05 were considered to be significant.

Results

BHR was more frequently found in subjects exposed to combustion products of domestic gas cooking appliances than in nonexposed subjects (21% *versus* 14%) (table 1). Prevalences of attacks of dyspnoea at rest (9% *versus* 5%) or chronic cough (12% *versus* 7%) were also significantly higher. The higher prevalence of asthma medication (4% *versus* 2%) was borderline, significant. The mean FEV_1 as a percentage of predicted (111% *versus* 114%) was lower in exposed subjects. Prevalences of current asthma

Table 1. – Characteristics of subjects by cooking

	Gas	Electric	p-value*
n	1664	257	
Area Groningen	35 (587)	14 (35)	
Area Roosendaal	37 (621)	43 (111)	<0.01
Area Geleen	27 (456)	43 (111)	
Males	53 (877)	48 (124)	0.18
Mean age yrs	44 (20–70)	43 (20–70)	0.49
Current smokers	38 (636)	30 (76)	0.01
Bronchial hyperresponsiveness	21 (342)	14 (37)	0.02
Mean FEV_1 % pred.	111	114	<0.01
Current asthma	2 (34)	2 (5)	0.92
Use of asthma medication	4 (72)	2 (5)	0.07
Wheeze	21 (348)	16 (41)	0.07
Attacks of dyspnoea at rest	9 (150)	5 (12)	0.02
Chronic cough	12 (191)	7 (18)	0.03
Symptoms of allergic rhinitis	31 (521)	31 (80)	0.95
Pos. spec. IgE	31 (523)	39 (100)	0.02
Pos. spec. IgE house dust mite	21 (354)	23 (60)	0.45
Pos. spec. IgE cat	5 (90)	5 (14)	0.98
Pos. spec. IgE timothy grass	15 (244)	20 (50)	0.05
Pos. spec. IgE cladosporium	3 (55)	4 (11)	0.42
Pos. spec. IgE birch	10 (162)	16 (41)	<0.01
Geometric mean total IgE $kU \cdot L^{-1} \pm SD$	30±5	30±5	0.78
Use of extractor fan	68 (1129)	92 (236)	<0.01

Data are presented as percentage with number of patients in parentheses, unless otherwise indicated. FEV_1: forced expiratory volume in one second; pos.: positive; spec.: specific; IgE: immunoglobulin E. *: Chi-squared test.

and symptoms of allergic rhinitis and mean total IgE were equal among exposed and nonexposed subjects. Exposed subjects had lower prevalences of positive specific IgE to timothy grass and birch. Subjects who used gas for cooking were more frequently smokers (38% *versus* 30%) and less often used an extractor fan that takes the fumes outside the home while cooking (68% *versus* 92%).

Stratified by sex, the difference in prevalence of BHR between subjects using gas and subjects using electricity for cooking was statistically significant for females (24% *versus* 16%) but not for males (18% *versus* 13%) (table 2). Stratified by age group, the difference was only significant in subjects 20–44 yrs old (18% *versus* 10%) but not in subjects aged 45–70 yrs (24% *versus* 20%).

Stratification by total IgE with a cutoff point at the highest quartile, only gave a significant difference in subjects with high total IgE (33% *versus* 15%) and not in subjects with "normal" total IgE (17% *versus* 14%). Stratification by specific IgE to common inhalant allergens resulted in a significant difference in subjects with positive specific IgE (28% *versus* 16%) and not in subjects without specific IgE (17% *versus* 13%). Stratified by current smoking, the effect of gas cooking on bronchial hyperresponsiveness appeared to be borderline significant in nonsmokers only.

Figure 1 shows that the difference in prevalence of BHR between subjects who used gas and subjects who used electricity for cooking was especially high in subjects with high total IgE levels, independently of the presence of specific IgE to inhalant allergens.

Table 2. – Prevalences of bronchial hyperresponsiveness (BHR) by type of cooking stratified by sex, age group, total immunoglobulin (Ig)E level in the highest quartile, specific IgE to inhalant allergens, and current smoking

	Gas cooker		Electric cooker		
	n	BHR positive %	n	BHR positive %	p-value*
Males	877	18	124	13	0.19
Females	787	24	133	16	0.04
Aged 20–44 yrs	879	18	134	10	0.02
Aged 45–70 yrs	785	24	123	20	0.31
Total IgE lower 3 quartiles	1276	17	185	14	0.35
Total IgE highest quartile	388	33	72	15	<0.01
Specific IgE negative	1141	17	157	13	0.21
Specific IgE positive	523	28	100	16	0.02
Non smoker	1028	18	181	12	0.07
Current smoker	636	25	76	20	0.29

*: p-value of difference between gas and electric cooking (Chi-squared test with one degree of freedom). Bronchial hyperresponsiveness was defined as being present if the provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second was ≤2 mg.

Multiple linear regression analysis was performed with the dose-response slope of the bronchial provocation test as the dependent variable with adjustment for sex, age, cigarette smoking, use of extractor fan or unvented gasfires, and area of residence. This showed no effect of gas cooking on the dose-response slope of the bronchial provocation in subjects with a "normal" total IgE level, but a significant interaction term of gas cooking with total IgE (table 3). Thus, increased bronchial responsiveness with

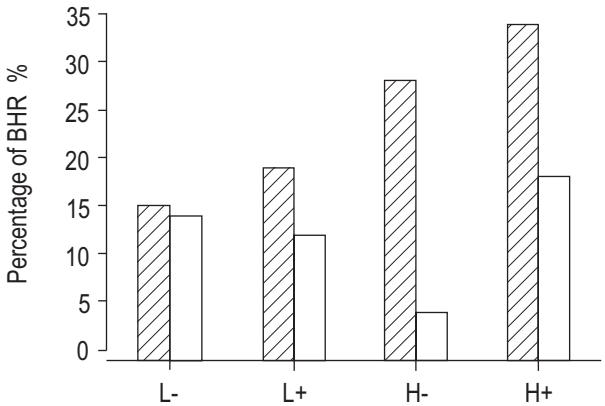

Fig. 1. – Prevalence of bronchial hyperresponsiveness (BHR) stratified by total immunoglobulin (Ig)E levels and specific IgE to inhalant allergens. ▨: subjects cooking on gas; □: subjects cooking on electricity; L-: low IgE and specific IgE negative; L+: low IgE and specific IgE positive; H-: high IgE and specific IgE negative; H+: high IgE and specific IgE positive.

Table 3. – Results from multiple linear regression analysis of the dose-response from gas cooking

Independent variable	Coefficient	Standard error	p-value
Constant	0.93	0.05	<0.01
Gas cooking*	-0.02	0.04	0.56
Gas cooking and high total IgE*	0.24	0.08	<0.01
Gas cooking and specific IgE*	0.13	0.07	0.06
Total IgE highest quartile*	-0.04	0.07	0.60
Specific IgE to inhalant allergens*	0.01	0.07	0.90
Use unvented gas for water heating*	-0.03	0.04	0.36
Extractor fan use*	-0.08	0.03	<0.01
Current smoking*	0.11	0.02	<0.01
Female sex*	0.12	0.02	<0.01
Age-45 yrs	0.01	0.00	<0.01
Area Limburg *versus* Groningen*	-0.03	0.03	0.29
Area Brabant *versus* Groningen*	-0.06	0.03	0.04

The dose-response slope was the percentage fall in forced expiratory volume in one second divided by the total dose of methacholine, $\log_{10}$ (slope +3) as the dependent variable. *: coded, "yes"=1 and "no"=0. IgE: immunoglobulin E.

gas cooking was only found in subjects with a high total IgE level. This effect was independent of the presence of specific IgE to inhalant allergens. The dose-response slope was also associated with gas cooking in subjects with specific IgE to inhalant allergens, although it became only borderline significant when adjustment was made for total IgE.

Subjects who used an extractor fan had a significantly lower dose-response slope. The number of subjects with high total IgE who used an electric cooker without an extractor fan was too small [5] to study whether the association between bronchial responsiveness and type of cooking was significantly modified by extractor fan use by including an interaction term in the model of table 3. In subjects who used gas for cooking, the prevalence of BHR was significantly lower in users of an extractor fan that takes the fumes outside the home than in subjects who never used a fan (18% *versus* 27%; $p<0.01$).

According to the model of table 3, a 45 yr old nonsmoking male from the area Groningen with specific IgE to inhalant allergens and a high total IgE level has a predicted decline in FEV_1 of 24% after a dose of 2 mg of methacholine when gas is used for cooking together with an extractor fan without using an unvented gas fire for water heating. A decline of 7% is predicted when electricity is used for cooking. A female with the same characteristics has a predicted decline of 33% when using gas and 11% when using electricity.

Table 4 shows the results of four separate linear regression models, one model for each possible combination of high/low total IgE and the presence/absence of specific IgE, after adjustment for the same variables mentioned in table 3. A significant effect of gas cooking on bronchial responsiveness was only found in the group of subjects with both specific IgE to inhalant allergens and a high total IgE level. This group also showed the greatest protective effect of the use of an extractor fan. An increased bronchial responsiveness in current smokers was only found in the other three groups that appeared to be less susceptible to the effect of gas cooking (table 4).

The relationship between gas cooking and the dose-response slope was not significantly different for males and females when tested by including an interaction term into the model of table 3. Age did not modify the relationship either.

Additional adjustment for reported home characteristics, such as age of the house, recent home damping or water damage, type of heating and furnishing or "age at which full time education was completed" showed that these factors did not confound the relationship between type of cooking and dose-response slope (data not shown).

Discussion

This study has shown that the use of gas for cooking is associated with BHR in subjects with high total IgE levels.

Several epidemiological studies have described adverse health effects of gas cooking without identifying a susceptible group of subjects. Gas cooking has been shown to be associated with a higher prevalence of respiratory symptoms or illnesses [1, 2, 6] and with small reductions in lung function [4]. JARVIS *et al.* [11] found that females who had specific IgE to inhalant allergens were at greater risk of symptoms if they cooked with gas than females who were nonatopic. This difference, however, did not reach statistical significance. The current results show that total IgE better identifies susceptible subjects than the presence of specific IgE.

This epidemiological study supports the findings of laboratory-based studies that have demonstrated that exposure to pollutants such as O_3 and NO_2 can enhance the airway response of particularly susceptible subjects such as asthmatic or atopic persons to inhaled allergen [18–21]. This is also supported by the finding of BOEZEN *et al.* [28] that children with both a high total IgE level and BHR are especially susceptible to short-term effects of ambient air pollution [28]. The mechanisms underlying these effects are not fully understood. Recent studies suggest that airway epithelial cells of atopic subjects show an increased ability to express, synthesize and release proinflammatory mediators [29, 30]. Exposure to combustion products of gas cooking might induce inflammation of the airways in atopic subjects with subsequent development of BHR.

Experimental animal research suggests that air pollution may induce airways epithelial damage and impaired mucocillary clearance which allows easier penetration and access of inhaled allergens to cells of the immune system [31]. Experimental exposure to ambient levels of NO_2 in asthmatics has shown enhancement of the allergen-induced late asthmatic reaction [21]. Some epidemiological studies supported these theories by showing a higher prevalence of sensitization in more polluted areas [32, 33]. However, the present study did not show enhancement of sensitization as a consequence of gas cooking. On the contrary, a lower prevalence of sensitization in subjects exposed to combustion products of domestic gas appliances was found. Higher prevalences of gas cooking

Table 4. – Results of four separate linear regression models of the effects of gas or electric cooking on bronchial hyperresponsiveness

	High total IgE				Low total IgE			
Independent variable	Specific IgE Coefficient ±SEM	p-value	No specific IgE Coefficient ±SEM	p-value	Specific IgE Coefficient ±SEM	p-value	No specific IgE Coefficient ±SEM	p-value
n	318		156		323		1179	
Gas cooking	0.37±0.10	<0.01	0.13±0.12	0.32	0.06±0.07	0.42	-0.01±0.04	0.77
Extractor fan	-0.31±0.08	<0.01	0.01±0.09	0.95	-0.13±0.07	0.05	-0.01±0.03	0.86
Current smoking	-0.11±0.07	0.12	0.31±0.08	<0.01	0.12±0.05	0.02	0.13±0.02	<0.01
Unvented gas	-0.21±0.14	0.12	0.14±0.12	0.25	-0.07±0.09	0.42	0.00±0.04	0.91

Results of four separate linear regression models of the effects of gas or electric cooking on bronchial hyperresponsiveness. Coefficients±SEM, and p-values for gas cooking, extractor fan use, current smoking, and unvented gas fire for waterheating from multiple linear regression with the dose-response slope (log 10 (slope+3)) as dependent variable after stratification for total immunoglobulin (Ig)E and specific IgE. (A separate model for each combination of high or low total IgE and the presence or absence of specific IgE (four models) with adjustment for sex, age, and area of residence.)

together with lower prevalences of sensitization in the area Groningen compared to the other two areas appeared to be responsible for this.

The absence of objective measurements of NO_2 in most epidemiological studies has been proposed as an explanation for the inconsistent findings of adverse effects of gas cooking. However, studies evaluating the association between NO_2 and respiratory symptoms have likewise been inconsistent [2, 15]. In the Netherlands lower lung function parameters with increasing NO_2 exposure were found [15]. Recently, PILOTTO *et al.* [16] suggested that short-term peaks of NO_2 might be more important than averaged levels over 1–2 week periods, which may explain the inconsistency of the association between NO_2-exposure and respiratory symptoms.

BHR, attacks of dyspnoea and chronic cough all are significantly more prevalent among exposed subjects (Table 1), however, current asthma is not. An explanation for this apparent inconsistency may be that gas cooking does not directly cause asthma. Exposure to the combustion products of gas cooking may increase the severity of asthma which can be measured as the degree of BHR. The presence of a high total IgE level probably identifies subjects predisposed to asthma who are susceptible to this adverse effect of gas cooking.

This study did not show a sex difference in the association between gas cooking and bronchial responsiveness. If the effect of gas cooking is related to exposure to high levels of combustion products, females who generally do most of the cooking, would be the group most at risk. Indeed, JARVIS *et al.* [11] found larger associations in females than in males in some countries.

Higher prevalences of other unknown risk factors of respiratory illness among persons from households with domestic gas appliances cannot be excluded. This study gave no indication that known differences in home characteristics or socioeconomic status between households with both types of cooking are responsible for the found relationship. Adjustment for several home characteristics and type of heating in multiple regression analysis did not influence the association between bronchial responsiveness and type of cooker. Adjustment for "the age at which full time education was completed", which generally gives an indication of socioeconomic status, did not weaken the relationship either.

Since acceptance criteria for bronchial provocation excluded subjects with a heart disease or β-blocker use, some selection of younger subjects has occurred (complete data were obtained from 46% of the age group 20–44 yrs and 39% of the age group 45–70 yrs). Besides which, the results of a postal screening questionnaire about respiratory symptoms that was sent to all of the subjects before they were invited to the examination, showed that there was a tendency of subjects with symptoms of tightness in the chest, attacks of dyspnoea at night and asthma-attacks to become nonresponders (for tightness in the chest the prevalence was 16% in nonresponders compared to 13% in responders; for nightly attacks of dyspnoea: 12% *versus* 9%; for asthma-attacks: 4% *versus* 2%). Both selections may have influenced prevalences. However, the authors find it unlikely that the studied association between gas cooking and respiratory health would be different for subjects excluded from this analysis.

In conclusion, this study has shown that the use of gas cooking is associated with bronchial hyperresponsiveness in subjects with high total immunoglobulin E levels. The results suggest that exposure to combustion products of gas cooking only affects respiratory health in susceptible subjects characterized by the presence of atopy. Differences in proportions of susceptible subjects studied may explain why the results of previously performed epidemiological studies concerning adverse effects of gas cooking are inconsistent.

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