Stroke and Use of Low-Dose Oral Contraceptives in Young Women
A Pooled Analysis of Two US Studies

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Background and Purpose—The available data on low-dose oral contraceptive pill (OCP) use and stroke risk in US women are limited by small numbers. We sought more precise estimates by conducting a pooled analysis of data from 2 US population–based case-control studies.

Methods—We analyzed interview data from 175 ischemic stroke cases, 198 hemorrhagic stroke cases, and 1191 control subjects 18 to 44 years of age.

Results—For ischemic stroke, the pooled odds ratio (pOR) adjusted for stroke risk factors for current use of low-dose OCPs compared with women who had never used OCP (never users) was 0.66 (95% confidence interval [CI], 0.29 to 1.47) and compared with women not currently using OCPs (nonusers) the pOR was 1.09 (95% CI, 0.54 to 2.21). For hemorrhagic stroke, the pOR for current use of low-dose OCPs compared with never users was 0.95 (95% CI, 0.46 to 1.93) and compared with nonusers the pOR was 1.11 (95% CI, 0.61 to 2.01). The pORs for current low-dose OCP use and either stroke type were not elevated among women who were ≥35 years, cigarette smokers, obese, or not receiving medical therapy for hypertension. pORs for current low-dose OCP use were 2.08 (95% CI, 1.19 to 3.65) for ischemic stroke and 2.15 (95% CI, 0.85 to 5.45) for hemorrhagic stroke among women reporting a history of migraine but were not elevated among women without such a history. Past OCP use (irrespective of formulation) was inversely related to ischemic stroke but unrelated to hemorrhagic stroke.

Conclusions—Women who use low-dose OCPs are, in the aggregate, not at increased risk of stroke. Studies are needed to clarify the risk of stroke among users who may be susceptible on the basis of age, smoking, obesity, hypertension, or migraine history. (Stroke. 1998;29:2277-2284.)

Key Words: contraceptives, oral ■ stroke, hemorrhagic ■ stroke, ischemic ■ women
among women enrolled in the Northern and Southern California Kaiser Permanente Medical Care Plans,1 and the other study was conducted among women residing in 3 counties in western Washington State.2 These studies provide the only data addressing the risk of stroke among current users of low-dose oral contraceptives in the United States. The study designs, including recruitment plans and data collection instruments, were developed independently by investigators at the 2 sites. However, because the investigators expected the incidence of stroke in young women to be low in both populations, the 2 groups consulted during the design phases to establish plans for pooled analyses of the data from the 2 studies. These analyses would theoretically permit more extensive and precise examination of the relationship between OCP use and stroke than could be achieved at either study site alone. This report describes the results of these pooled analyses.

Subjects and Methods
Detailed descriptions of the methods of each of the 2 studies have been published.1,4 Both studies included cases of myocardial infarction (MI) in addition to stroke. The major features of each study as they relate to analyses of OCP use and stroke, as well as the methods for pooling and analyzing the data, are reported here.

Case Definition, Identification, and Recruitment
Kaiser Permanente Study
Eligible cases were all 18 to 44-year-old female members of the Kaiser Permanente (KP) Medical Care Plans of Northern and Southern California diagnosed with incident stroke from May 1991 through August 1994 (Northern California) or July 1991 through August 1994 (Southern California). Potentially eligible cases were identified through review and abstraction of medical records at all acute care hospitals serving the 3 counties, supplemented with monthly letters to neurologists, neurosurgeons, and physiatrists, and regular review of death certificates. Of 249 eligible cases identified in the KP study, of whom 357 patients or proxies (89%) were interviewed for the study.

University of Washington Study
Eligible cases were all 18- to 44-year-old female residents of King, Pierce, or Snohomish counties, Washington, who were free of major clinical coronary heart disease and cerebrovascular disease and who were diagnosed with stroke between July 1991 and February 1995. Potentially eligible cases were identified through discharge diagnoses and review and abstraction of medical records at all acute care hospitals serving the 3 counties, supplemented with monthly letters to neurologists, neurosurgeons, and physiatrists, and regular review of death certificates. Of 249 eligible cases identified in the University of Washington (UW) study, 183 patients or their proxies (73%) were interviewed.

In both studies, incident stroke was defined as the new, rapid onset of symptoms and signs consistent with loss of brain function that lasted at least 24 hours and could not be ascribed to subdural hematoma, brain tumor, infection, seizure, or other neurological disease such as multiple sclerosis. For this analysis, confirmed incident strokes were first classified as either of arterial or venous origin. Arterial strokes were further subclassified as hemorrhagic events, ischemic events, or other, which included arterial dissections. Hemorrhagic strokes were further classified according to location of bleed (subarachnoid versus intracerebral). In the KP study, 2 physicians reviewed medical records to establish eligibility and classify potential cases, with discrepancies in their classification reviewed by a single board-certified neurologist. In the UW study, a single board-certified neurologist reviewed the records to establish eligibility and classify potential cases. A reliability substudy demonstrated high agreement (89.5%) between the 2 approaches in the classification of patients as having had a stroke (versus no stroke) and complete concordance as to stroke type (hemorrhagic versus ischemic) among stroke patients who were classified in these 2 categories.

Control Definition, Identification, and Recruitment
Kaiser Permanente Study
For each case patient, 3 control subjects matched on exact year of birth and facility of usual care were selected from among women who were KP Medical Care Program members in the same calendar year that the case’s stroke occurred. An attempt was made to recruit 3 interviewed controls per interviewed case. The response rate among first-identified controls was 76%.

University of Washington Study
A set of 18- to 44-year-old female residents of King, Pierce, and Snohomish counties during the case diagnosis period was selected for comparison with both stroke and MI cases. These women were identified using random-digit telephone dialing, with stratified recruitment that mirrored the combined age distribution of the stroke and MI cases. Only women who were free of major clinical coronary heart disease and cerebrovascular disease were included. The response rate incorporating both the household screening phase of random-digit dialing and the in-person interview phase was 73%.

Sources of Information and Definition of Variables
Cases and controls in both studies participated in structured in-person interviews to obtain information on OCP use as well other known or suspected cardiovascular risk factors. When a case patient was unable to participate due to death or mental impairment, we interviewed a proxy respondent. Written informed consent was provided by all participants; data collection procedures were approved by the institutional review boards of the KP Medical Care Plans and the UW. All information was collected for the period prior to each woman’s predefined reference date, which was the date of stroke onset for cases. For a control, the reference date was either the same date as the stroke onset date of the case to which she was matched (KP study) or a randomly assigned date selected from among the possible stroke onset dates (UW study). In the KP study, a woman was considered a current OCP user if she reported that she was taking OCPs in the month before reference date. In the UW study, OCP use was ascertained according to calendar months. To ensure that women who were using OCPs in the month before reference date were included as current users, we classified a woman from the UW study as a current user if she reported taking OCPs in either the same calendar month as her reference date or the calendar month before her reference date. In each study, a woman was classified as a past OCP user if she had used OCPs but did not meet the definition of a current user. The remaining women were classified as having never used these medications. Although the interview instruments used in the 2 studies were not identical, we judged that the questions used to obtain information on OCP use and key cardiovascular risk factors used similar wording and response coding schemes to permit pooling of the data. The most substantial difference in wording was for the question on history of migraine headaches: in the KP study, each woman was asked whether a doctor had ever said that she had had a migraine headache, whereas in the UW study, each woman was asked if she had ever visited a doctor for a migraine headache.

Exclusions Prior to Data Pooling
For this pooled analysis we excluded cases and controls from the KP study who had reported a history of myocardial infarction or other major coronary heart disease; such women were not eligible for the UW study. We also excluded from this analysis stroke patients who had not been directly interviewed because we determined that proxy respondents provided inaccurate information as to whether or not the patient had used OCPs in the past. Finally, we excluded patients whose strokes were not classified as ischemic or hemorrhagic, and cases and controls who were pregnant at diagnosis or for whom
information on OCP use status as of diagnosis (current, past, or never) was missing. When a case from the KP study was excluded for 1 of the above reasons, we excluded her matched controls as well. The number of cases (or proxy respondents of cases) interviewed in each study and excluded before this analysis is shown in Table 1. Among the hemorrhagic stroke cases, 133 were subarachnoid in origin, 49 were intracerebral in origin, and the remainder (16) were either of mixed or uncertain origin.

### Statistical Analysis

Each of the 2 study teams created a data set of the individual records for interviewed cases and controls. The variables were coded according to a common protocol developed after joint review of the data collection instruments from each study. The respective data sets were merged to create a single pooled data set for these analyses. We used the method of Moreno et al.\(^7\) to estimate pooled odds ratios (pORs) for oral contraceptive use and stroke, accounting for the matched design of the KP study and the unmatched design of the UW study. This approach ensures that the exposure status of cases and controls is compared within each study, and for the KP Study, within matched sets. In addition, adjustment for confounding is based on an identical set of covariates. Briefly, a single logistic regression model was fit in which the UW data contributed to an unconditional likelihood function and the KP data contributed to a conditional likelihood function. The unconditional and conditional likelihood functions were multiplied to obtain the joint likelihood function. Coefficients for the logistic model were obtained by maximizing the logarithm of the joint likelihood with use of the Newton-Raphson algorithm. Ninety-five percent confidence intervals (CIs) on the ORs were estimated from standard errors of the

### Table 1. Distribution of Stroke Cases by Inclusion Status and Study and Stroke Type

<table>
<thead>
<tr>
<th>Inclusion Status</th>
<th>Kaiser Permanente</th>
<th>University of Washington</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interviewed*</td>
<td>165</td>
<td>63</td>
</tr>
<tr>
<td>Not included in analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior history of heart disease</td>
<td>19</td>
<td>...</td>
</tr>
<tr>
<td>No direct interview</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Missing data†</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pregnant at reference date</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>No matched control</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Included in analysis</td>
<td>121</td>
<td>54</td>
</tr>
</tbody>
</table>

*Direct or proxy interviews. There were 28 stroke cases (16 KP, 12 UW) for whom direct or proxy interviews were conducted that were not classified as ischemic stroke or hemorrhagic stroke. These cases, which were excluded from the analysis, consisted of 15 arterial dissections, 9 venous strokes, and 4 strokes that could not be classified as to type.

†Whether or not the woman was a current, past, or never user of oral contraceptives.

### Table 2. Demographic and Cardiovascular Risk Factors Among Stroke Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ischemic Stroke (n=175)</th>
<th>Hemorrhagic Stroke (n=198)</th>
<th>Controls (n=1191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>37.7±5.8</td>
<td>36.3±6.1</td>
<td>37.4±5.9</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>52.0</td>
<td>54.0</td>
<td>66.0</td>
</tr>
<tr>
<td>Black</td>
<td>25.7</td>
<td>21.7</td>
<td>8.7</td>
</tr>
<tr>
<td>Hispanic white</td>
<td>14.3</td>
<td>15.2</td>
<td>11.9</td>
</tr>
<tr>
<td>Asian</td>
<td>3.4</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Other and unknown</td>
<td>4.6</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>42.9</td>
<td>41.4</td>
<td>30.2</td>
</tr>
<tr>
<td>College</td>
<td>52.6</td>
<td>50.0</td>
<td>57.9</td>
</tr>
<tr>
<td>Graduate studies</td>
<td>4.6</td>
<td>8.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Treated hypertension, %</td>
<td>20.6</td>
<td>10.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Treated diabetes, %</td>
<td>14.9</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Current cigarette smoking, %</td>
<td>35.4</td>
<td>39.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>20.6</td>
<td>14.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Body mass index* of ≥27.3</td>
<td>53.7</td>
<td>34.3</td>
<td>30.4</td>
</tr>
<tr>
<td>Migraine headaches</td>
<td>29.9</td>
<td>25.8</td>
<td>19.3</td>
</tr>
<tr>
<td>Alcohol consumption ≥1/d, %</td>
<td>4.6</td>
<td>8.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Vigorous exercise ≥2/w, %</td>
<td>19.4</td>
<td>30.0</td>
<td>37.9</td>
</tr>
</tbody>
</table>

*Weight in kilograms divided by square or height in meters.
†Average frequency in year prior to reference date.
coefficients. All models included a minimum set of covariates, consisting of terms for cigarette smoking, current treatment for hypertension, menopausal status, and ethnicity. We examined the potential for further confounding by additional variables by estimating associations with and without adjustment for these characteristics. Terms were retained in the model if they caused a meaningful change (10% to 15%) in the pOR for the particular OCP use variable examined. The specific covariates included in each model are reported in the footnotes to Tables 2 through 5. We tested the assumption that the ORs for OCP use were homogeneous across the 2 studies by fitting separate models for the KP and UW data, and then using Wald’s $\chi^2$ tests for the equality of regression coefficients. Stratum-specific pORs were obtained by including indicator terms representing women who were both current low-dose OCP users and who possessed the following known or suspected stroke risk factors: age (35 years), current smoking, body mass index (BMI) $\geq 27.3$ kg/m$^2$, and history of migraine headache. To test hypotheses that the risk of stroke associated with low-dose oral contraceptive use differed among women with and without these characteristics, we performed hierarchical likelihood ratio tests to obtain p-values for heterogeneity of the pORs.

**Results**

Table 2 shows the distribution of cases and controls according to demographic and cardiovascular risk factors. Ischemic stroke cases and hemorrhagic stroke cases were less likely to be Asian, and more likely to be African-American, to have had fewer years of education, to be receiving treatment for hypertension, be current cigarette smokers, and to be postmenopausal than controls. Treated diabetes and obesity (BMI
of $27.3$ kg/m$^2$) were more common among ischemic stroke cases compared with controls. Ischemic stroke patients, and to a lesser extent hemorrhagic stroke patients, were more likely to report a history of migraine compared with controls. Daily alcohol consumption was more common among hemorrhagic stroke cases than controls. Regular vigorous exercise was less common among stroke cases than controls, particularly for ischemic stroke.

For ischemic stroke, the adjusted pooled OR for current use of low-dose OCPs ($50$ µg ethinyl estradiol) compared with women not currently using OCPs was $1.09$ (95% CI, 0.54 to 2.21) (Table 3). Compared with never users, the pORs were below $1$ for both current use of low-dose OCPs (pOR, 0.66; 95% CI, 0.29 to 1.47) and past use of any oral contraceptives (pOR, 0.51; 95% CI, 0.70 to 0.88). The results for current low-dose OCP use and hemorrhagic stroke were similar (Table 3), but past use of OCPs was not associated with hemorrhagic stroke (pOR, 0.82; 95% CI, 0.50 to 1.35). With the exception of the results for past use of OCPs and hemorrhagic stroke, the study-specific ORs were very simi-
lar. There were too few subjects who reported current use of high-dose oral contraceptives (>50 μg) (2 ischemic stroke cases; 2 hemorrhagic stroke cases, and 7 controls) for meaningful analyses.

Table 4 shows the adjusted pORs in relation to specific features of past OCP use and current low-dose OCP use. For neither stroke type did the pORs exhibit a trend with increasing duration of use. There was no statistical evidence of heterogeneity across study sites in the associations with duration of use. There was no statistical evidence of heterogeneity in these results across the 2 studies. For ischemic stroke, the pORs for current use of norgestrel-type progestin OCPs (those containing norgestrel or levonorgestrel) were essentially the same as the pORs for norethindrone-type progestin OCPs (those containing norethindrone, norethindrone acetate, ethynodiol diacetate, or norethynodrel) (Table 4). For hemorrhagic stroke, the pORs for current use of norgestrel-type progestins were elevated whereas the pOR was < 1 for current use of norethindrone-type progestins; these estimates were based on small numbers and were not statistically significant. Although there was no statistically significant heterogeneity between the data of the 2 studies, only the UW data suggested an elevated association for hemorrhagic stroke associated with current use of OCPs with norgestrel-type progestin (data not shown).

Compared with women who were not current users of OCPs, the pORs for ischemic stroke in relation to current use of low-dose OCPs were < 1 among older women, women who were current cigarette smokers, and women who were obese (Table 5). For hemorrhagic stroke there was no difference in the pORs according to these characteristics. There was no association between current use of low-dose OCPs and either ischemic or hemorrhagic stroke among women not receiving treatment for hypertension. There were too few women receiving treatment for hypertension and who were current OCP users (1 ischemic stroke case, 0 hemorrhagic stroke cases, and 2 controls) to permit meaningful analyses. All of the confidence intervals on the pORs according to age, cigarette smoking, obesity, and hypertension status included one. For both types of stroke the pORs were approximately 2 among women with a history of migraine headache, whereas the pORs were not increased among women without such a history. The confidence intervals on the pORs for women with a history of migraine headache, however, overlapped considerably the respective CIs for
women without such a history. All of the differences in pORs across strata of stroke risk factors were highly consistent with random variation ($P\geq 0.33$) based on the likelihood ratio tests.

**Discussion**

The risks of stroke were not increased among current users of low-dose OCPs in this pooled analysis of 2 US population–based case-control studies. The pOR for ischemic stroke and past use of OCPs was significantly $<1.0$, whereas the pOR for hemorrhagic stroke and past use of OCPs was not $<1.0$. Although the pORs for current and past use were generally the same as the ORs from the individual studies, combining the data from the 2 studies improved the precision of the estimates, as indicated by the narrowed CIs. There was no strong evidence of trends in pORs with recency of use or duration of use among past or current users. Age, obesity, and cigarette smoking did not appear to modify the relation between OCP use and stroke. The pORs appeared to be elevated among women who reported a history of migraine headaches.

A strength of this pooled analysis is that both studies were population based, and the incidence of stroke was similar in the populations (approximately 11 per 100,000 women-years). Identical definitions of ischemic and hemorrhagic stroke were used by the 2 studies, and we confirmed that the definitions were applied reliably despite differences in the approach to classification. Limitations to this pooled analysis include the different ethnic compositions of the 2 populations and the limited statistical power to detect heterogeneity in the ORs between the 2 studies.

We excluded stroke patients who could not be directly interviewed, and we cannot dismiss the possibility that our results have been affected by an influence of OCP use on the severity of stroke. The study-specific estimates reported here for current and past use are similar to those previously published from analyses that included proxy respondents, so restriction to self-respondents is unlikely to have caused a serious bias in our results. Other limitations of the individual studies, including potential recall bias and nonparticipation bias, apply to this analysis as well.

Our results for current use of low-dose OCPs compared with nonusers contrast with those reported from the European sites of the World Health Organization multinational case-control study (OR, 1.5 for ischemic stroke and 1.3 for hemorrhagic stroke). Since the WHO studies observed increased risks among cigarette smokers and women who had not had a recent blood pressure measurement and little or no association among nonsmokers or women who had had a recent blood pressure measurement, some of the differences in these findings may be due to a higher prevalence of cigarette smoking and hypertension among OCP users in Europe. Compared with women who had never used OCPs, our results for ischemic stroke differ considerably from the OR of 1.9 reported from a Danish case-control study of cerebral thromboembolic attack. That the Danish study excluded stroke patients with known risk factors, whereas our case definition was more inclusive, could account for the differences. Finally, given that the majority of hemorrhagic strokes in our sample were subarachnoid in origin, our results for hemorrhagic stroke are broadly consistent with a report from a case-control study of subarachnoid hemorrhage.

Previous studies have reported inconsistent results regarding the risk of stroke among women who are not current users but who had used OCPs in the past. Our results for ischemic stroke broadly agree with those of a Danish study of cerebral thromboembolic attack in which there was a statistically significant inverse association with past use. In contrast, the absence of an association between past use and hemorrhagic stroke differ from that in a previous US study in which an inverse association was found for subarachnoid hemorrhage. Results of analyses of past OCP use are difficult to interpret because of variation in the availability of different formulations over time and across populations. The absence of a trend in the pORs with duration of use provides some evidence that the observed inverse association between past use and ischemic stroke does not represent a true protective effect. Instead, it may be that women currently of childbearing age who previously used OCPs have been “selected” for a very low risk of stroke in ways that we could not adequately measure, and thus control, in this study.

Epidemiological and clinical studies have raised the possibility that the occurrence of arterial vascular disease among OCP users might be increased among users of pills containing levonorgestrel (which composes 50% of norgestrel by weight) as opposed to norethindrone-type progestins, We observed an elevated pOR for norgestrel-type progestins only for hemorrhagic stroke. These analyses were based on very small numbers of cases, and thus we are not able to draw any definitive conclusions regarding the relationship, if any, between the progestin component of low-dose OCPs and stroke risk.

The major contraindications to prescribing low-dose OCPs—cigarette smoking and hypertension—are based on early epidemiological studies of cardiovascular disease in users of OCPs containing ethinyl estradiol (see, for example, References 15 and 16). Despite pooling of data, our study population included relatively few current users of low-dose OCPs who also were cigarette smokers or were treated for hypertension. Thus, our analyses had limited power to clarify whether these contraindications apply to US women who use low-dose OCPs. In the absence of more precise data from US populations, results from other studies justify maintaining the current contraindications to prescribing low-dose OCPs.

Several complex issues must considered when interpreting findings among women with migraine headaches in this and previous studies. Associations may be spurious if women with hemiplegic migraine are erroneously included as stroke cases or if women using OCPs were more likely to be told or to believe they had migraine headaches when in fact they were experiencing early stroke symptoms. This latter possibility might explain the elevated pOR we observed for hemorrhagic stroke, since there is minimal evidence that these cerebrovascular events are related to a history of migraine headaches. Alternatively, the true association with low-dose OCP use among women with migraine may be higher, because we relied on relatively imprecise methods to classify women according to migraine history. In
addition, there are 2 issues specific to this analysis. First, because the ascertainment of migraine history differed in the 2 studies, the validity of pooling the data is debatable. Second, given the overlapping CIs and the results of formal tests of heterogeneity, the pORs for women with and without a history of migraine headaches cannot be distinguished statistically. Taken together, while our data are consistent with other reports\textsuperscript{17} that low-dose OCP use may be associated with an increased risk of stroke among women with a history of migraine headaches, no firm conclusions can be drawn given the potential biases and limited statistical power in available studies.

Low-dose OCPs are highly effective methods of reversible contraception that have additional, well-established noncontraceptive health benefits.\textsuperscript{18} Our data indicate that the risk of stroke, in general, is not increased among US women who use low-dose OCPs. In our population, the stroke rate is approximately 11\times 10^{-5} women per year,\textsuperscript{1,4} and 10\% of the women similar in age to stroke patients are current users of low-dose OCPs. Thus, even if the true relative risk is approximately 2 (the upper bound of the 95\% CIs on the pORs for current use), at most 1 additional stroke occurs per 10\textsuperscript{5} 18- to 44-year-old women in the population because of the use of low-dose OCPs. Future studies will need to clarify the characteristics of women who might be particularly susceptible to stroke when using low-dose OCPs. For the vast majority of young women, however, we conclude that low-dose OCPs are safe with respect to stroke, since the contraceptive and noncontraceptive benefits outweigh the potential risk of cerebrovascular disease.

References
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