APPENDIX A.

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I. ENDPOINTS.

A. Venous thromboembolism (deep venous thrombosis and pulmonary embolism)

1. Identification of potential cases

Computerized data were screened to identify potential cases. Potential diagnoses were identified from hospital admissions, outpatient visits, and death certificates. Diagnosis codes are shown in Table S1.

Table S1. Diagnosis Codes for identification of possible cases of venous thromboembolism *

Diagnosis	ICD-9 codes	ICD-10 codes*
Deep venous thrombosis	451.1, 451.1x, 451.2, 451.8, 451.81, 451.82, 451.84, 451.89, 453.0, 453.1, 453.2, 453.3, 453.4x, 453.8, 453.9	I80-I82
Pulmonary embolism	415.1	I26

*For mortality

2. Medical record review of potential cases

For potential cases, trained medical record abstractors reviewed records of all hospital-based care encounters around the time of the potential event, including emergency department and hospital records and autopsy reports where applicable. Information collected included presenting symptoms, results of imaging studies, and interventions undertaken (e.g., anticoagulant therapy, placement of filter, thrombectomy).

3. Adjudication of potential cases.

Deep Venous Thrombosis (DVT)

Hospitalized DVT

In order to be labeled DEFINITE, DVT required:
1. Hospital discharge summary with a diagnosis of deep vein thrombosis (ICD-9 codes 451.1. 451.1x, 451.2, 451.8x, 451.9, 453.0, 453.1, 453.2, 453.8, 453.9), and;
2. Positive venographic study.

Reported DVT documented by positive impedance plethysmography or Doppler exam or radioisotope scan, sonogram, or other non-invasive test examination only were considered PROBABLE

Hospital discharge summary with a primary discharge code of DVT without documentation of positive venographic study or non-invasive test examination will be considered POSSIBLE.

Hospital discharge summary with a secondary discharge code of DVT without documentation of positive venographic study or non-invasive test examination will be considered to be a non-event.

Both definite and probable DVTs were utilized as study endpoints in the analysis.

Outpatient DVT

Outpatient DVT was included as a POSSIBLE event if:
1. Outpatient diagnosis of deep venous thrombosis and:

Outpatient DVT (cont.)

2. First prescription for an anticoagulant (low-molecular weight heparin preparation or warfarin) during the 30 day period subsequent to the diagnosis.

The medical records of outpatient DVTs were abstracted as part of the main study. A substudy was conducted at the Oakland site to determine the validity the DVT diagnosis as assessed in the outpatient setting.

Pulmonary Embolism (PE)

In order to be labeled DEFINITE, PE required:
1. Hospital discharge summary with a diagnosis of pulmonary embolism (ICD-9 codes 415.1) and a positive pulmonary arteriogram or CT angiogram.
2. Death certificate diagnosis of pulmonary embolism with autopsy findings consistent with pulmonary embolism.

PE was defined as PROBABLE in case of:
1. Hospital discharge summary with a primary diagnosis of pulmonary embolism without a positive pulmonary arteriogram or CT angiogram, or
2. Ventilation – perfusion scan showing > 2 segmental perfusion defects without ventilation defect (from WHI), and diagnosis of deep vein thrombosis (DVT) based on meeting > 1 DVT criterion plus signs and symptoms suggestive of PE (e.g. acute chest pain, dyspnea, tachypnea, hypoxia, tachycardia, or chest x-ray findings) or
3. Spiral CT scan, and diagnosis of deep vein thrombosis (DVT) based on meeting > 1 DVT criterion plus signs and symptoms suggestive of PE (e.g. acute chest pain, dyspnea, tachypnea, hypoxia, tachycardia, or chest x-ray finding, or
4. Death certificate diagnosis of pulmonary embolism without autopsy.

Two physicians adjudicated the events. A second review was performed on a random 10% sample of records as well a second review and discussion of all records that were not considered to be complete clear-cut in regards to the diagnosis.

B. Acute Myocardial Infarction

1. Clinical Definition

Myocardial infarction is defined as the death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombosis, or the rupture of a plaque. The definition will require meeting the definition of myocardial infarction used in the Atherosclerotic Risk in Communities (ARIC) study includes a combination of clinical symptoms accompanied by diagnostic cardiac enzyme elevation or electrocardiogram changes. (*White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. J Clin Epidemiol 1996;49:223-33*) with the electrocardiogram changes interpreted by the study cardiologist.

2.. Identification of potential cases.

Initial Identification of Events. Acute myocardial infarction (MI) were identified from principal hospital discharge diagnoses of ICD-9 code 410.x, as well as ICD-10 (I21.x, I22.x) codes from death certificates.

Medical record review. Trained medical records abstractors will gather and review records of all hospital-based care encounters around the time of the potential event, including emergency department and hospital records and autopsy reports when available in the medical record. Chart reviewers made

B. Acute Myocardial Infarction (cont.)

copies of the following for subsequent clinical adjudication: EMS/ambulance notes, ED notes, admit H&P, all cardiology consult notes, all ECGs (not rhythm strips), all cardiac labs, cardiovascular procedures, and discharge summary.

3. Medical record review of potential cases

For potential cases, trained medical record abstractors reviewed records of all hospital-based care encounters around the time of the potential event, including emergency department and hospital records and autopsy reports where applicable. Information collected include presenting symptoms, presenting vital signs, laboratory investigation including cardiac enzymes, results of electrocardiograms, results of angiography, and interventions undertaken (angioplasty, bypass surgery, or thrombolytic therapy) .

4. Adjudication

Two physicians adjudicated the events, one a cardiologist and the other an internist trained in preventive cardiology and with extensive experience in adjudicating cardiovascular disease endpoints for research studies. The cardiologist reviewed all records with duplicate review of a random 10% sample of records by the second adjudicator as well a second review and discussion of all records that were not considered to be complete clear-cut in regards to the diagnosis.

The adjudication of myocardial infarctions utilized a combination of clinical symptoms, blood biomarkers, and ECG findings in an algorithm to categorization a medical hospitalization as a definite myocardial infarction (MI), probable MI, suspect MI or no MI as shown in Table S2. This algorithm was adapted from the ARIC study algorithm to allow for the use of cardiologist interpretation of the ECG rather than ECG coding. The use of the algorithm is supported by Dr. Wayne Rosamond, one of the clinical endpoint lead investigators at the ARIC Coordinating Center.

Table S2. Algorithm for MI categorization of a medical hospitalization.

Chest pain PRESENT				**ECG Evidence**	**Chest pain ABSENT**			
Definite MI	Definite MI	Definite MI	Definite MI	Diagnostic	Definite MI	Definite MI	Definite MI	Definite MI
Definite MI	Probable MI	Suspect MI	No MI	Suspicious	Probable MI	Suspect MI	No MI	No MI
Definite MI	Probable MI	No MI	No MI	Equivocal	Suspect MI	Suspect MI	No MI	No MI
Probable MI	Suspect MI	No MI	No MI	Absent or uncodeable	Suspect MI	No MI	No MI	No MI
Abnormal	Equivocal	Incomplete	Normal		Abnormal	Equivocal	Incomplete	Normal
Biomarker		Evidence			Biomarker		Evidence	

Chest pain. The presence or absence of chest pain was noted.

Biomarkers. Cardiac biomarkers (troponin and/or CPK-MB) were considered abnormal if at least one value was great than twice the upper limit of normal for the laboratory and equivocal if at least one value was above the upper limit of normal and no values were greater than twice the upper limit of normal.

ECG criteria.

1. Diagnostic (in absence of LVH and LBBB).
    a. Evolving ST elevation or depression as per Universal Definition of MI:
        i. ST elevation – new ST elevation at the J-point in two contiguous leads with the cut-off points: ≥ mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads

   ii. ST depression and T-wave changes – new horizontal or down-sloping ST depression ≥0.05 mV two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wa or R/S ratio >1.
   b. New Q waves
   c. New left bundle branch block
2. Suspicious, new changes:
   a. T wave inversion without ST changes.
   b. Borderline ST changes (less than those specified for diagnostic ECG.
   c. New right bundle branch block.
3. Equivocal.
   a. New upsloping ST depression.
   b. ST elevation present but not in 2 contiguous leads or in presence of LVH.

C. Stroke

1. Clinical Definition

Stroke was defined as an acute neurologic deficit of sudden onset that persists more than 24 hours, corresponds to a vascular territory, and was not explained by other causes such as trauma, infection, vasculitis, extracranial hemorrhage leading to hypotension or profound hypotension from another cause.

2. Identification of potential cases

Computerized data were screened to identify potential cases. Potential diagnoses will be identified from hospital admissions and death certificates. Diagnosis codes are shown in Table S3.

Table S3. Diagnosis codes used to identify potential strokes

Group (Death certificates & 1^{o} hospital discharge diagnoses)	ICD-9 codes	ICD-10 codes
Subarachnoid hemorrhage	430	I60
Intracerebral hemorrhage	431	I61, I64
Nontraumatic extradural hemorrhage	432.0	I62.1
Unspecified intracranial hemorrhage	432.9	I62.0, I62.9
Occlusion and stenosis of precerebral arteries	433.x	I65
Occlusion of cerebral arteries	434.x	I63, I66
Acute, but ill-defined, cerebrovascular disease	436	I67, I68

The list of codes was intentionally broad to ensure complete ascertainment of possible cases.

3. Medical record review of potential cases .

For potential cases, trained medical record abstractors at each site reviewed records of all hospital-based care encounters around the time of the potential event, including emergency department and hospital records.

Information collected included presenting symptoms, radiologic evaluations, angiographic evaluations, and interventions undertaken, and patient disposition. Medical record abstractors recorded whether the patient had any prior neurologic events, including strokes. In addition, information was recorded from the clinical examination, including level of consciousness, strength of extremities, gait, and presence of dysarthria or aphasia, sensory deficits, double vision, forced gaze, dysphagia, seizures, dizziness/vertigo or evidence of impaired cognitive function.

C. Stroke (cont.)

4. Adjudication.

Two physicians adjudicated the events, one a neurologist and the other an internist with extensive experience in adjudicating stroke records. The neurologist reviewed all records with duplicate review of a random 10% sample of records by the second adjudicator as well a second review and discussion of all records that were not considered to be complete clear-cut in regards to the diagnosis.

The TOAST criteria will be used for categorizing ischemic stroke. Stroke is defined as the rapid onset of a headache, meningsmus or a persistent neurologic deficit attributable to an obstruction or rupture of the arterial system (including stroke occurring during a procedure such as angiography or surgery.) Deficit is not known to be secondary to brain trauma, infection, or other non-ischemic cause. Deficit must last more than 24 hours, unless death supervenes or there is a demonstrable lesion compatible with acute stroke on CT or MRI scan.

The definition of a stroke <u>excludes:</u>

- Headache alone and no demonstrated blood by LP, CT, or MRI scan;
- Bell's palsy or labyrinthine disease;
- Metabolic problems (such as diabetic, uremic or hepatic coma) as a cause of altered consciousness;
- Brain tumor as found by hospital course, CT or MRI scan, angiography, biopsy, or autopsy;
- Trauma by history, CT or MRI scan, or angiography
- Infection (encephalitis, abscess) by CT or MRI scan, LP, or absence of fever;
- Old stroke by CT or MRI scan. This is usually diagnosed if the location of the infarct is inappropriate to explain the findings or when there is nearby focal ventricular enlargement. Recent infarcts often have edema or show distortion of the brain, are enhanceable, or show progression between CT or MRI scans;
- Seizures with status and post-ictal paralysis (Todd's) by history or observation and history of past seizures. Sometimes when a stroke causes seizure, CT or MRI scan or angiogram can confirm the stroke;
- Venous infarcts and subdural hematomas; or
- Hysteria, which can usually be differentiated by inconsistencies on examination and evidence of secondary gain.

The assessment of DEFINITE stroke will be made based on 1) the final physician diagnosis that a stroke has occurred, and 2) the satisfaction of the appropriate algorithms.

Strokes will be subdivided into three types:

1. hemorrhagic
2. ischemic
3. unknown type stroke

<u>Hemorrhagic Stroke</u>

Must meet one or more of the following criteria:

1. Blood in subarachnoid space or intraparenchymal hemorrhage by CT or MRI scan. If intraparenchymal, blood must be dense and not mottled (mixed hyperdensity and hypodensity).
2. Bloody spinal fluid by lumbar puncture plus neurologic signs and symptoms consistent with stroke.
3. Death from stroke within 24 hours of onset and no LP, CT, MRI or autopsy (Death within 24 hours of stroke is nearly always due to hemorrhage.)

C. Stroke (cont.)

Hemorrhagic Stroke Subtypes

Hemorrhagic stroke is further divided into subarachnoid hemorrhage, intraparenchymal hemorrhage, and indeterminate hemorrhagic stroke.

Subarachnoid Hemorrhage

Must meet one or more of the following criteria:

1. Headache or coma or combination with possibly some focal deficit and CT or MRI shows subarachnoid blood in basal cistern, tissues or convexity or blood clots in these locations; may also see aneurysm or arteriovenous malformation with enhancement.
2. Similar clinical picture with bloody CSF. Headaches, stiffness and coma outweighs focal deficit; may have subhyloid hemorrhage, 3rd nerve palsy.
3. Autopsy evidence of subarachnoid hemorrhage.

Intraparenchymal Hemorrhage

Must meet one or more of the following criteria:

1. CT or MRI shows intraparenchymal increased density (not mottled); location is compatible with deficit,
2. Bloody CSF with progressive focal deficit, and
3. Autopsy evidence of intraparenchymal hemorrhage.

Indeterminate Type Hemorrhage Stroke

Must meet one or both of the following criteria:

1. Death within 24 hours of onset without evidence by CT or MRI, or surgery or autopsy of location of blood, and
2. Bloody LP but no definite clinical picture compatible with either subarachnoid or intraparenchymal hemorrhage.

Ischemic Infarction

Must meet one or more of the following criteria:

1. Focal brain deficit without CT, MRI or LP evidence of blood.
2. CT or MRI with mottled cerebral pattern or showing decreased density in a compatible location with reported symptoms and signs.
3. Surgical or autopsy evidence of ischemic infarction.

Ischemic Stroke Subtypes

Ischemic stroke is further divided into lacunar, embolic, atherosclerotic and other/unknown type of ischemic stroke.

Lacunar

Must meet one or more of the following criteria:

1. Angiogram, if done, shows evidence of adjacent major artery occlusion or severe stenosis and one of the following is present:
    a. CT or MRI shows a deep area of decreased density less than 2 cm in maximum length in a location compatible with the clinical picture;

C. Stroke (cont.)

Lacunar (cont.)

b. normal CT or MRI with clinical syndrome of pure motor hemiparesis, pure sensory stroke, ataxia hemiparesis and dysarthria clumsy hand syndrome; and;

c. autopsy evidence of lacunar stroke due to small vessel disease.

Embolic Stroke

Must meet one or more of the following criteria:

1. Cerebral hemisphere infarction with a recognized source for emboli or systemic emboli (including atrial fibrillation, endocarditis, mitral valve disease, clot in the heart by echocardiogram, CT or MRI, recent cardiac surgery or trauma, myocardial infarction). No lacunae by CT or MRI compatible with the clinical picture.
2. Hemorrhagic infarction (mottled) by CT or MRI.
3. CT or MRI showing small <1/2 lobe cortical infarction compatible with clinical findings, and no prior TIAs in the same territory.
4. Autopsy shows area of infarction thought to be due to embolus.

Atherosclerotic Infarction

Must meet one or both of the following criteria:

1. Focal infarct in the setting of evidence for large vessel disease, with no evidence of lacunar, mottled infarction, or small cortical infarct by CT or MRI and no sources of emboli and one of the following:
   a. preceding TIAs in the same vascular territory
   b. carotid artery bruit over the proximate artery
   c. internal carotid bifurcation if compatible, and
2. Autopsy evidence of infarction caused by atherosclerosis.

Unknown Type Stroke

Satisfies the criteria for stroke; inadequate information to categorize as hemorrhagic or ischemic.

Other/Unknown Infarction

Includes:

1. All cases not classified by the above rules for lacunar, embolic or atherosclerotic infarction;
2. All cases that could be classified in more than one of the above categories; and
3. All cases attributed to arteritis or dissection of the arterial wall.

II. EXCLUSIONS

Table S4. Study exclusions defined utilizing the following ICD9 and CPT codes as noted in study report section on exclusions (page 13)

Exclusions			
Medical condition	**ICD9 code**	**ICD9 Procedure code**	**CPT code**
Sickle cell disease	282.6		
Cancer (malignant neoplasms except non-melanoma skin)	140.00 – 172.9 and 174.00-209.00		
HIV	042, 043, 044, 79.53, V08		
Organ transplant	V42.0, V42.1, V42.6, V42.6, V42.7, V42.81, V42.83, 996.8	33.5, 33.6, 37.5, 41.0, 50.5, 52.8, 55.6	32851, 32852, 32853, 32854, 33935, 33940, 33945, 38240, 38241, 47135, 47136, 48554, 48556, 50320, 50360, 50365, 50380
Liver failure	570, 572.4, 572.8, 997.4		
Renal failure	585, 586, 996.1, V45.1, V56.0, 996.73	39.95, 54.98	36832, 36833, 36831, 90989, 90993, 90999, 90935, 90935, 90945, 90947, 90980, 90918, 90919, 90920, 90921, 90922, 90923, 90924, 90925
Respiratory failure	518.5, 518.81, 518.82	96.70, 96.71, 96.72	
Cystic fibrosis	277.0		
Cerebral palsy	343		
Heart failure	398.91, 404.01, 404.03, 404.11, 404.13, 428		
Pulmonary embolism	415.1		
Deep venous thrombosis	451.1, 451.2, 451.8, 451.9, 453.0, 453.1, 453.2, 453.3, 453.4, 453.8, 453.9,		
Acute myocardial infarction	410.x		
Stroke	430, 431, 432.0, 432.9, 433, 434, 436		

III. COVARIATES – Rationale for inclusion and listing of covariates

Covariates of interest were assessed during the 6-month pre-exposure eligibility period with assessment continuing throughout the exposure period. Each covariate was analytically managed in one of 3 ways:

a. **Current vs. not current**: Some medications that may impact the risk of cardiovascular disease endpoints were evaluated in this manner, so that exposure was considered to be present only on the dates when a dose was prescribed. In addition, some exposures (major injuries and surgeries) were considered to have an effect for only 6 weeks.
b. **Ever vs. never during exposure period**: Some medical conditions that were not considered to be chronic were categorized as being present from the date they were first noted though the remainder of the exposure period. For example, cardiac arrhythmias fell into this category.
c. Ever vs. never until end of study: Some medical conditions that were generally considered to be chronic were categorized as being present from the date they were first noted through the remainder of the study, i.e., throughout the exposure period in which they were identified through all subsequent exposure periods. For example, diabetes is condition that fell into this category.

Thus, each person-day of follow-up was classified using the study definitions below. For some time-varying dichotomous covariates, such as diagnoses of cardiovascular disease, substance abuse or cigarette smoking, a single appearance at any time during follow-up created a fixed value for that variable from that point forward.

The medical care encounters include both prescribed medications as well as diagnostic encounters (physician, emergency room, and inpatient encounters). These all refer to the medical care received during the pre-exposure eligibility period and exposure periods. Diagnostic encounters were classified according to the diagnoses codes present in the medical encounter.

Age and site were included as covariates the analytic assessment of outcomes. Five-year age groupings (10-14, 15-19, . . ., 45-59, 50-55) were used for the age adjustment.

Other covariates fall into several categories into the categories noted below: cardiovascular disease and CVD risk factors; other medical conditions: contraindications to DRSP; off-label uses of combined hormonal contraceptives.

1. Cardiovascular disease (CVD) and CVD risk factors.

Major risk factors available in the electronic medical data for ischemic heart and cerebrovascular diseases included hypertension, hyperlipidemia, and diabetes mellitus. Atrial fibrillation is a major risk factor for ischemic stroke and other cardiac dysrhythmias may increase risk for CVD.

Other relatively common medical conditions including asthma, chronic obstructive pulmonary disease (COPD), and chronic kidney disease have been shown to increase the risk of CVD.

Tobacco cigarette use is a risk factor for all 3 study endpoints, but was poorly ascertained in all of the study databases for most of the study period and was not included as a convariate.

Obesity is a risk factor for venous thromboembolic disease and is a contributory factor to cardiovascular risk factors (diabetes, hypertension, dyslipidemia). Body mass index (BMI) and obesity were also poorly ascertained in the study databases and were not included as covariates.

2. **Other Medical Conditions (coagulation disorders, cocaine/psychostimulant dependence and abuse)**

Thombophilic disorders may be potential confounders is the associations of CHC use with venous thromboembolic disease. Cocaine is a risk factor for ischemic cardiovascular disease and other psychostimulants may be, probably due to their vasoconstrictive and blood-pressure elevating effects. Thyroid disease, varicose veins, and seizure disorders (epilepsy) have been noted in other studies and were included as covariates.

3. **Contraindications to DRSP.**

Contraindications to DRSP included renal insufficiency, hepatic dysfunction, and adrenal insufficiency . With the exception of hepatic dysfunction, these contraindications were unique among the study CHCs to DRSP and were evaluated as potential confounders.

4. **Off-label uses of combined hormonal contraceptives.**

CHCs may be used in the treatment of some medical conditions including mild to moderate acne, polycystic overy syndrome (PCOS), dysmenorrhea, menorrhagia, endometriosis, irregular menstrual cycles / dysfunctional uterine bleeding, and adenomyosis. With the exception of PCOS, none of these conditions is known to be associated with cardiovascular disease and VTE. Women with PCOS tend to have higher levels of cardiovascular risk factors, with nearly 40% having impaired glucose tolerance or diabetes, and a higher prevalence of subclinical cardiovascular disease as assessed by coronary artery calcification (CAC) and carotid intima medial thickness measurement (IMT). PCOS (ICD-9 code 256.4) was therefore included as a potential confounder (confounding by indication) in assessing the risk of CVD associated with CHCs, and we also tested the associations of others as potential covariates.

5. Surgery and injuries.

Immobilization and trauma may place individuals at increased risk for cardiovascular disease endpoints, most notable VTE. Each of the hospitalizations for the surgical events and injuries listed in Table 1 was considered as a covariate with a current effect of 6 weeks.

A summary of the definitions and the analytic approach for each of the covariates (except medications) is shown in Supplement **Table S5**, below.

Table S5. Summary of non-medication covariates and analytic approach.

Covariate	Criteria for condition	Analytic approach		
		Current vs. not current	Ever vs. never during exposure	Ever vs. never until end of study
Cardiovascular disease and CVD risk factors				
Diabetes mellitus	Date of diagnosis from diabetes registry; or Two outpatient visits and or hospitalizations with following code: 250.x; or One outpatient visit or hospitalization with 250.x code and one prescription for hypoglycemic medication within 6 months; or Two prescriptions for hypoglycemic medication;			X
Hypertension	Two outpatient visits: 401x-405x (hypertensive disease); or One outpatient visit with 401x-405x code and one prescription for anti-hypertensive medication within 6 months.			X
Hyperlipidemia	Two outpatient visits (any combination of the following codes): 272.0, 272.2, 272.4; or One outpatient visit with code 272.0, 272.2, 272.4 and one prescription for non-statin antilipemic medication within 6 months; or Two prescriptions for non-statin antilipemic medications.			X
Other ischemic heart disease	Principal hospital discharge codes of 411-414, 429.7; or $\geq$1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses with above codes.			X
Atrial fibrillation	Principal hospital discharge diagnosis code of 427.31; or $\geq$1 emergency room diagnosis of 427.31; or at least 2 outpatient diagnoses with 427.31		x	
Other cardiac dysrhythmias	Principal hospital discharge diagnosis code of 427.31; or $\geq$1 emergency room diagnosis of 427.31; or at least 2 outpatient diagnoses with 427.31.		x	
Heart failure	Principal hospital discharge codes of 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.13, 404.91, or 404.93, 428.x; or $\geq$1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses with above codes.			X
Transient ischemic attack	Principal hospital discharge diagnosis code of 435; or $\geq$1 emergency room diagnosis of 435.		x	
Migraine	Principal hospital discharge diagnosis code of 346.xx; or $\geq$1 emergency room diagnosis of 346.xx; or at least 2 outpatient diagnoses with 346.xx.		x	

Table S5. (cont)

Covariate	Criteria for condition	Analytic approach		
		Current vs. not current	**Ever vs. never during exposure**	**Ever vs. never until end of study**
Cardiovascular disease and CVD risk factors (cont.)				
Peripheral vascular disease	Principal hospital discharge codes of 440.2, 440.3, 443, 444.2, 444.8, 445.0, 785.4; or ≥1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses with above codes.			X
Chronic obstructive pulmonary disease (COPD)	Principal hospital discharge codes of 491, 492, 496; or ≥1 emergency room diagnosis with above codes; or at least 2 outpatient diagnoses with above codes.			X
Systemic lupus erythematosis	Two outpatient visits and or hospitalizations with following code: 710.0			X
Chronic kidney disease	Principal hospital discharge codes of 585.x; or ≥1 emergency room diagnosis of 585.x; or at least 2 outpatient diagnoses of 585.x.			X
Other medical conditions				
Coagulopathy (thombophilia)	Principal hospital discharge codes of 286.9; ≥1 emergency room diagnosis of 286.9; or at least 2 outpatient diagnoses of 286.9.			X
Asthma	Principal hospital discharge codes of 493; or ≥1 emergency room diagnosis of 493; or at least 2 outpatient diagnoses of 493.		x	
Cocaine dependence/abuse	Principal hospital discharge codes of 304.2, 305.6; or ≥1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses of above codes.		x	
Amphetamine and other psychostimulant dependence/abuse	Principal hospital discharge codes of 304.4, 305.7; or ≥1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses of above codes.304.4, 305.7		x	
Thyroid disorders	Principal hospital discharge codes of 242.x; or ≥1 emergency room diagnosis of 242.x; or at least 2 outpatient diagnoses of 242.x.		x	
Varicose veins of lower extremity	Principal hospital discharge codes of 454.x; or ≥1 emergency room diagnosis of 454.x; or at least 2 outpatient diagnoses of 454.x.		x	
Epilepsy	Principal hospital discharge codes of 345.x; or ≥1 emergency room diagnosis of 345.x; or at least 2 outpatient diagnoses of 345.x.		x	

Table S5. (cont)

Covariate	Criteria for condition	Analytic approach		
		Current vs. not current	**Ever vs. never during exposure**	**Ever vs. never until end of study**
Contraindications to Yasmin				
Renal insufficiency	Principal hospital discharge codes of 584-586, 595.3, 997.5; or ≥1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses of above codes		x	
Hepatic dysfunction	Principal hospital discharge codes of 570-572, 573.1, 573.2, 573.8, 573.9; or ≥1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses of above codes.		x	
Adrenal insufficiency	Principal hospital discharge codes of 255.4, 255.5; or ≥1 emergency room diagnosis of above codes; or at least 2 outpatient diagnoses of above codes.		x	
Off-label uses of CHCs				
Polycystic ovary syndrome	Principal hospital discharge codes of 485.x or at least 2 outpatient diagnoses of 485.x.			X
Acne	Two outpatient visits and or hospitalizations with following code: 706.1		x	
Off-label uses of CHCs				
Dysmenorrhea	Two outpatient visits and or hospitalizations with following code: 625.3		x	
Premenstrual tension syndromes	Two outpatient visits and or hospitalizations with following code: 625.4		x	
Major surgeries*	***Surgeries have current effect for 6 weeks**			
Operations on the respiratory system (30-34)	**Procedure code during a hospitalization**			
Excision Of Larynx	30	x		
Other Operations On Larynx And Trachea	31	x		
Excision of lung or bronchus	32	x		
Other operations on lung or bronchus	33	x		
Operations on chest wall, pleura, mediastinum, and diaphragm	34	x		

Table S5. (cont.)

Covariate	Criteria for condition	Analytic approach		
		Current vs. not current	**Ever vs. never during exposure**	**Ever vs. never until end of study**
Operations on the cardiovascular system (35-39)		x		
Operations On Valves And Septa Of Heart	35	x		
Operations On Vessels Of Heart	36	x		
Other Operations On Heart And Pericardium	37	x		
Incision, Excision, And Occlusion Of Vessels	38	x		
Other Operations On Vessels	39	x		
Operations On The Hemic And Lymphatic System (40-41)				
Operations On Lymphatic System	40	x		
Operations On Bone Marrow And Spleen	41	x		
Operations on the Digestive System (42-54)				
Operations On Esophagus	42	x		
Incision and Excision of Stomach	43	x		
Other Operations on Stomach	44	x		
Incision, Excision and Anastomosis of Intestine	45	x		
Other operations on Intestine	46	x		
Operations on Appendix	47	x		

Table S5. (cont.)

Covariate	Criteria for condition	Analytic approach		
		Current vs. not current	**Ever vs. never during exposure**	**Ever vs. never until end of study**
Operations on the Digestive System (42-54) (cont)				
Operations On Rectum, Rectosigmoid, And Perirectal Tissue	48	x		
Operations on Anus	49	x		
Operations On Liver	50	x		
Operations On Gallbladder And Biliary Tract	51	x		
Operations On Pancreas	52	x		
Repair Of Hernia	53	x		
Other Operations On Abdominal Region	54	x		
Operations On The Urinary System (55-59)				
Operations On Kidney	55	x		
Operations On Ureter	56	x		
Operations On Urinary Bladder	57	x		
Operations On Urethra	58	x		
Other Operations On Urinary Tract	59	x		
Operations on uterus				
Hysterectomy	68.4-68.7	x		
Pelvic evisceration	68.8	x		
Obstetrical procedures (72-75)				
All obstetrical procedures	72-75	x		

Table S5. (cont.)

Covariate	Criteria for condition	Analytic approach		
		Current vs. not current	**Ever vs. never during exposure**	**Ever vs. never until end of study**
Operation on the musculoskeletal system (76-84)				
Spinal fusion	81.0	x		
Arthoplasty of knee and ankle	81.4	x		
Arthroplasty of hip	81.5-81.6	x		
Amputation of lower limb	84.1	x		
Injuries*	***Injuries have current effect for 6 weeks**			
Condition	**Diagnosis code during a hospitalization, outpatient visit, or emergency room visit.**			
Fracture of vault of skull	800	x		
Fracture of base of skull	801	x		
Fracture of vertebral column	805-806	x		
Fracture of pelvis	808	x		
Fracture of neck of femur	820	x		
Fracture of other and unspecified parts of femur	821	x		
Fracture of patella	822	x		
Fracture of tibia and fibula	823	x		
Fracture of ankle	824	x		
Other, multiple, and ill-defined fractures of lower limb	827	x		
Multiple fractures involving both lower limbs, lower with upper limb, and lower limb(s) with rib(s) and sternum	828	x		
Cerebral laceration and contusion	851	x		

Table S5. (cont.)

Covariate	Criteria for condition	Analytic approach		
		Current vs. not current	Ever vs. never during exposure	Ever vs. never until end of study
Injuries (cont)				
Subarachnoid, subdural, and extradural hemorrhage, following injury.	852	x		
Other and unspecified intracranial hemorrhage following injury	853	x		
Intracranial injury of other and unspecified nature	854	x		
Internal injury of chest, abdomen, and pelvis	860-869	x		
Third degree burn of lower limb(s)	945.3, 945.4, 945.5	x		
Third degrees burns of multiple specified sites	946.3, 946.4, 946.5	x		
Spinal cord injury without evidence of spinal bone injury	952	x		
Certain early complications of trauma (e.g. air embolism, fat embolism, traumatic shock)	958	x		

6. Pharmacy medications

Pharmacy medications will be assessed as covariates for several purposes:

1. To support the definition of cardiovascular risk factors (hypertension, hyperlipidemia, and diabetes mellitus as defined earlier). Once present, these covariates are considered to be present until the end of study follow-up.
2. Medications that are typically used for the secondary prevention of cardiovascular disease whether or not they are used to support the definition of a cardiovascular risk factor (statins, ACE inhibitors, angiotensin receptor blockers, beta blockers) were considered to present during current use.
3. Medications that interact with DRSP or have potential to increase serum potassium (NSAIDs, potassium-sparing diuretics, potassium supplements, ACE inhibitors, angiotensin-II receptor antatgonists, heparin) were considered to be present during current use.

6. **Pharmacy medications (cont.)**

4. Anticoagulant medications impact on the risk of venous thromboembolic disease and possibly of the other study disease endpoints and were considered to be present during current use

5. While it is unlikely that estrogen replacement/hormone replacement therapy (ERT/HRT) will be initiated during CHC use, it is possible that it will occur especially in the period of time after termination of CHC. ERT/HRT increases the risk of venous thromboembolism and may impact the risk of MI and stroke and was considered to be present during current use.

A medication may be considered in more than one category, e.g. an ACE inhibitor might support the diagnosis of hypertension (category #1) as well as being used for the secondary prevention of cardiovascular diseases (category #2).

The prescription periods for medications in each of the following classes were determined and used to define the prescriptions period(s) for that class (Table 2). Thus, if the women's record included prescriptions for two different statins (e.g., lovastatin, simvastatin) both prescriptions would be used to determine the statin prescription period(s) that women.

A list of the **National Product Codes (NPCs)** for the medications is included as **Appendix C.**

Table S6. Medications

ACE inhibitors, alone or in combination	benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Angiotensin receptor blocker	losartan, valsartan, irbesartan, telmisartan, candesartan, eprosartan, olmesartan
Beta-blockers	acebutol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol
Calcium channel blockers	dihydropyridines (nifedipine, nicardipine, felodipine, isradipine, nisoldipine, amlodipine, nimodipine), bepridil, verapamil, diltiazem
Diuretics, loop	furosemide, bumetanide, torsemide, ethacrynic acid
Diuretics, potassium-sparing	amiloride, triamterene, spironolactone
Diuretics, other	thiazide (hydrochlorothiazide, chlorothiazide, chorthalidone, bendroflumethiazide, polythiazide, methylchlothiazide, metolazone, indapamide,), acetazolamide, dichlorphenamide, glycerin, mannitol, urea
Hypoglycemics, insulin	lispro, aspart, glulisine, NPH or lente, ultralente, glargine, detemir, isophane, regular, zinc
Hypoglycemics, oral	sulfonylureas (acetohexamide, tolazamide, chloropropamide, tolbutamide, glipizide, glyburide, glimepirde), biguanide (metformin), alpha-glucosidase inhibitor (acarbose, miglitol), thiazolinedione (rosiglitazone, pioglitazone, troglitazone), other (repaglinide, liraglutide, nateglinide, exenatide), pramlintide, sitagliptin)
Lipid lowering drugs, statins	lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, cerivastatin
Lipid lowering drugs, other	fibrate derivates (clofibrate, gemfibrozil, fenofibrate), bile acid sequestrants (cholestyramine, colestipol, colesevelam), cholesterol absorption inhibitors (ezetimibe), niacin, (niacin+lovastatin, niacin+simvastatin)
NSAIDs including COX2 inhibitors	bromfenac, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone naproxen, oxaprozin, piroxicam, sulindac, tolmetin, COX2 inhibitors (celecoxib, rofecoxib, valdecoxib)
Other antihypertensives	aliskiren, alpha 1 blockers (prazosin, terazosin, doxazosin, , phenoxybenzamine), reserpine, centrally acting sympatholytic agents (methyldopa, clonidine, guanabenz, guanfacine), hydralazine, guanethidine, eplerenone, guanadrel, deserpidine, metyrosine, minoxidil, mecamylamine
Platelet inhibitors, not aspirin alone	ticlopidine, clopidogrel, dipyridamole, eptifibatide, cilostazol, aspirin-dipyridamole
Anticoagulants, warfarin	warfarin
Anticoagulants, low molecular weight (LMW) hepain	dalteparin, enoxaparin, tinazparin
Anticoagulants, heparin	heparin
Anticoagulants, other	anisinindion, argatroban, bivalirudin, dicumarol, fondaparinux, lepirudin
Hormone replacement	conjugated estrogens, conjugated estrogens synthetic A, conjugatedestrogens synthetic B, diethylstilbestrol, esterified estrogens, estradiol, estradiol micronized, estradiol acetate, estradiol cypionate, estridiol valerate, estrone, estropipate, ethinyl estradiol, estriol micronized, conjugated estrogens-methyltestosterone, esterified estrogen-methyltestosterone, estradiol and testosterone cypionates, conjugated estrogens-medroxyprogesterone acetate, estradiol-norethindrone acetate, north
Potassium replacement	potassium acetate, potassium bicarbonate, potassium chloride