EPID 765 METHODS AND ISSUES IN PHARMACOEPIDEMIOLOGY

3 credits

*PRE*-requisites: EPID 600 and BIOS 600 or equivalents

Lead-Instructor: Til Stürmer; sturmer@unc.edu; 919 966 7433

Co-Instructor: Michele Jonsson Funk; mfunk@unc.edu; 919-843-0384

January 10 – April 25, 2019

Tuesday, Thursday, 2:00 – 3:15

Room: Rm MGG 2301

Pharmacoepidemiology: Application of epidemiologic knowledge, methodology, and reasoning to the study of the effects (beneficial and adverse) and uses of drugs in human populations

Pharmacoepidemiology is a public health discipline that mainly relies on non-experimental (epidemiologic) methods to assess intended and unintended drug effects to support decision-makers in the absence of specific evidence from experimental studies (randomized controlled trials). This course is for clinicians, pharmacists, epidemiologists and scientists from related fields in academia, industry and regulatory agencies. It will provide an introduction and overview of pharmacoepidemiologic topics, methods, databases, and review examples of current research. The course will look at specific aspects and potential pitfalls of epidemiologic study designs when applied to the study of drug effects and provide an overview of ways to limit the potential for bias.

Course objectives: introduce participants to most important issues and career options in pharmacoepidemiology; acquire basic understanding of how non-experimental studies on drugs can draw from standard epidemiologic techniques and unique research challenges and opportunities. Provide the tools necessary to evaluate published pharmacoepidemiologic studies and to design and implement (note: additional courses/skills required) pharmacoepidemiologic studies using state-of-the-art methodology to limit the potential for bias.

Structure: Journal club discussion, lectures, case studies, invited speakers. The course is organized as a sequence of relevant topics. Most lessons will start with a 30 minute discussion of the topic followed by a 45 minute lecture. Discussions are either student led (journal club) or led by the instructors. Preparation and active participation in the discussion is expected from all.
Grasp of challenges and concepts is encouraged over knowledge about solutions. Readings are from a draft PE textbook by the lead instructor, from the Textbook of Pharmacoepidemiology (see below), and from the literature.

**Expectations:**

- All students are expected to read required materials (all provided on Sakai) before class and to participate actively in class discussions. Suggested readings are intended for future reference.
- All students will lead a journal club discussion. I will ask for volunteers but may need to assign students.
- All students are expected to write a term paper on a pharmacoepidemiologic topic (see below).

**Grading:**

30%: Class participation
30%: Presentation and discussion of journal club article
40%: Term paper

Each will be graded on a 4 point scale
- 4: fully acceptable by professional colleague
- 3: evidence of a colleague in training
- 2: some merit but insufficient for scientific interchange
- 1: unacceptable or incomplete

An overall grade of at least 2.5 is required for a pass; students with a grade of 3.5 or higher will receive an honor grade.

**Journal Club presentation:**

During the last 20 minutes of class. The student will provide a brief summary of the paper (3 minutes, absolutely not more than 5!) and then lead the discussion. The discussion should cover important aspects of methods, results, and conclusions. Do not try to cover everything, but rather focus on specific aspects of these. Are the conclusions supported by the data presented? Would you change clinical practice based on the data presented?

**Term paper:**

The term paper should provide an overview of a chosen drug-outcome association. This is not to imply that the field of pharmacoepidemiology is restricted to this kind of study but rather to acknowledge that many challenges when addressing drug-outcome associations using non-experimental methods are unique to the field.

The paper should develop the history of the evidence ideally from case-report (or any other form of signal) to the current state of knowledge. The paper should indicate an understanding of the advantages and disadvantages of specific studies based on their design and analytic methodology, make a non-formal summary of the evidence taking design and analytic methodology into account, discuss limitations of the existing evidence and whether and how
these can be addressed, and finally propose possibilities to overcome evidence gaps based on existing or new data.

The overview should be based on the published literature and not cover a topic that has been recently reviewed (2013 or later) because that leaves little room for additional work and interpretation. For those taking the database class we encourage choosing the same topic but this is not necessary. A maximum of 4 students can team up for the term paper. For group term papers, we expect a qualitatively more substantial contribution and that students within a group evaluate their respective contributions.

Each student should submit a very brief (1 paragraph, max. 250 words) proposal for a topic indicating why this topic was chosen and whether it is suited to address the above mentioned points. These brief proposals are due 2/27 to allow discussion of problems/alternatives in the week before the spring break. Each student will need an agreed upon topic before the spring break (by 3/7). Each student will present their paper in class at the end of the course. We will have approximately 10 minutes per student/project including discussion (the final time will be a function of the number of projects/teams). The presentation will be limited to 5 minutes and 6 slides, sharp. The term paper is due 4/8 at midnight.

The term paper should conform to the instructions for authors of Pharmacoepidemiology and Drug Safety (review category, maximum 3,000 words). In addition, there should be at least one figure and not more than 3 tables. All facts presented should be referenced and any plagiarism avoided. Some of these papers may lead to publications while others will not.

The term papers will be graded based on the understanding of the difficulties to make decisions about the benefit and harm of a specific drug/drug class in the presence of less than ideal data, limitations of the existing evidence, and the proposal to overcome these. The latter should be based on an understanding of real life constraints (rather than “we propose a RCT enrolling 100k people to be treated over 20 years”). General statements (“could be biased”) should be avoided. Instead, an assessment of the direction and magnitude of potential biases of a specific study in relation to other studies should be made [e.g., “Study A did not control for SES. Low SES (defined as) vs. high SES (defined as) has been shown to be a risk factor for Y (RR;95%CI)[reference] and to be associated with barriers to receiving treatment B vs. C (OR;95%CI) [reference]; thus not controlling for SES would tend to bias the RR of B vs. C on Y in the direction of X and based on the strength of associations described above, the magnitude of bias would likely be sufficient to explain the observed result/discrepancies”].
Course Policies and Resources

Recognizing, Valuing and Encouraging Inclusion and Diversity in the Classroom

We share the School’s commitment to diversity. We are committed to ensuring that the School is a diverse, inclusive, civil and welcoming community. Diversity and inclusion are central to our mission — to improve public health, promote individual well-being and eliminate health inequities across North Carolina and around the world. Diversity and inclusion are assets that contribute to our strength, excellence and individual and institutional success. We welcome, value and learn from individual differences and perspectives. These include but are not limited to: cultural and racial/ethnic background; country of origin; gender; age; socioeconomic status; physical and learning abilities; physical appearance; religion; political perspective; sexual identity and veteran status. Diversity, inclusiveness and civility are core values we hold, as well as characteristics of the School that we intend to strengthen.

We are committed to expanding diversity and inclusiveness across the School—among faculty, staff, students, on advisory groups, and in our curricula, leadership, policies and practices. We measure diversity and inclusion not only in numbers, but also by the extent to which students, alumni, faculty and staff members perceive the School’s environment as welcoming, valuing all individuals and supporting their development.”

In this class, we practice these commitments in the following ways:

• Develop classroom participation approaches that acknowledge the diversity of ways of contributing in the classroom and foster participation and engagement of all students.
• Structure assessment approaches that acknowledge different methods for acquiring knowledge and demonstrating proficiency.
• Encourage and solicit feedback from students to continually improve inclusive practices.

As a student in the class, you are also expected to understand and uphold the following UNC policies:

Diversity and Inclusion at the Gillings School of Global Public Health: http://sph.unc.edu/resource-pages/diversity/
Prohibited Discrimination, Harassment, and Related Misconduct at UNC: https://deanofstudents.unc.edu/incident-reporting/prohibited-harassmentsexual-misconduct

Accessibility

UNC-CH supports all reasonable accommodations, including resources and services, for students with disabilities, chronic medical conditions, a temporary disability, or a pregnancy complication resulting in difficulties with accessing learning opportunities. All accommodations are coordinated through the UNC Office of Accessibility Resources &
Services (ARS), https://ars.unc.edu/; phone 919-962-8300; email ars@unc.edu. Students must document/register their need for accommodations with ARS before accommodations can be implemented.

Counseling and Psychological Services

CAPS is strongly committed to addressing the mental health needs of a diverse student body through timely access to consultation and connection to clinically appropriate services, whether for short or long-term needs. Go to their website: https://caps.unc.edu or visit their facilities on the third floor of the Campus Health Services building for a walk-in evaluation to learn more.

UNC Honor Code

As a student at UNC-Chapel Hill, you are bound by the university’s Honor Code, through which UNC maintains standards of academic excellence and community values. It is your responsibility to learn about and abide by the code. All written assignments or presentations (including team projects) should be completed in a manner that demonstrates academic integrity and excellence. Work should be completed in your own words, but your ideas should be supported with well-cited evidence and theory. To ensure effective functioning of the Honor System at UNC, students are expected to:

Conduct all academic work within the letter and spirit of the Honor Code, which prohibits the giving or receiving of unauthorized aid in all academic processes.

Learn the recognized techniques of proper attribution of sources used in written work; and to identify allowable resource materials or aids to be used during completion of any graded work.

Sign a pledge on all graded academic work certifying that no unauthorized assistance has been received or given in the completion of the work.

Report any instance in which reasonable grounds exist to believe that a fellow student has violated the Honor Code.

Instructors are required to report suspected violations of the Honor Code, including inappropriate collaborative work or problematic use of secondary materials, to the Honor Court. Honor Court sanctions can include receiving a zero for the assignment, failing the course and/or suspension from the university. If you have any questions about your rights and responsibilities, please consult the Office of Student Conduct at https://studentconduct.unc.edu/, or consult these other resources:

Honor system module.
UNC library’s plagiarism tutorial.
UNC Writing Center handout on plagiarism.

Recommended parallel course: Because pharmacoepidemiology relies heavily on the use of large automated healthcare databases, participants are encouraged to also take EPID 766 “Epidemiologic Research with
Healthcare Databases” taught in spring 2019 (Lead-Instructor: Dr. Jennifer Lund). Students are also encouraged to come to the Pharmacoepidemiology Seminar on Mondays, 3:30-4:30.

Available in the library for this course. This is a reasonably priced textbook providing a good overview, including overview of often used healthcare databases. You can get one for <$20.

Selection of and some comments on other pharmacoepidemiology textbooks:


Provides the reader with an overview of pharmacoepidemiology, as well as the epidemiology of specific disease states. Includes an annotated bibliography of pharmacoepidemiologic studies as of 20 years ago. A little old, ~$25


Selection of epidemiology textbooks


<table>
<thead>
<tr>
<th>#</th>
<th>Day</th>
<th>Date</th>
<th>Contents</th>
<th>Instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thu</td>
<td>1/10</td>
<td>What is pharmacoepidemiology?</td>
<td>TS</td>
</tr>
<tr>
<td>2</td>
<td>Tue</td>
<td>1/15</td>
<td>Sources of data for PE</td>
<td>Mitch Conover</td>
</tr>
<tr>
<td>3</td>
<td>Thu</td>
<td>1/17</td>
<td>Drug, outcome, and comorbidity data</td>
<td>TS</td>
</tr>
<tr>
<td>4</td>
<td>Tue</td>
<td>1/22</td>
<td>Methodologic Challenges in PE</td>
<td>TS</td>
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<tr>
<td></td>
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<td></td>
<td>• Confounding (by indication, frailty)</td>
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<td></td>
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<td>• Selection bias (healthy initiator, sick stopper, healthy user)</td>
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<tr>
<td>5</td>
<td>Thu</td>
<td>1/24</td>
<td>Study Design Solutions</td>
<td>TS</td>
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<td></td>
<td></td>
<td></td>
<td>• New user design</td>
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<td></td>
<td></td>
<td></td>
<td>• Active comparators</td>
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<tr>
<td>6</td>
<td>Tue</td>
<td>1/29</td>
<td>Risk periods</td>
<td>TS</td>
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<td></td>
<td></td>
<td></td>
<td>• First treatment carried forward</td>
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<td></td>
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<td></td>
<td>• As treated</td>
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<td></td>
<td></td>
<td>• Induction, carry-over, lag periods</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Thu</td>
<td>1/31</td>
<td>Propensity scores</td>
<td>TS</td>
</tr>
<tr>
<td>8</td>
<td>Tue</td>
<td>2/5</td>
<td>Disease risk scores</td>
<td>TS</td>
</tr>
<tr>
<td>9</td>
<td>Thu</td>
<td>2/7</td>
<td>Non-uniform treatment effects</td>
<td>TS</td>
</tr>
<tr>
<td>10</td>
<td>Tue</td>
<td>2/12</td>
<td>Instrumental variables</td>
<td>TS</td>
</tr>
<tr>
<td>11</td>
<td>Thu</td>
<td>2/14</td>
<td>Validation Studies</td>
<td>TS</td>
</tr>
<tr>
<td>12</td>
<td>Tue</td>
<td>2/19</td>
<td>Crystal ball PE, immortal time bias, immeasurable time bias</td>
<td>TS</td>
</tr>
<tr>
<td>13</td>
<td>Thu</td>
<td>2/21</td>
<td>Adherence &amp; persistence</td>
<td>TS</td>
</tr>
<tr>
<td>14</td>
<td>Tue</td>
<td>2/26</td>
<td>Patients treated contrary to prediction</td>
<td>TS</td>
</tr>
<tr>
<td></td>
<td>We</td>
<td>2/27</td>
<td>Term paper proposal</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Thu</td>
<td>2/28</td>
<td>Variability in treatments &amp; variable selection (including hdPS)</td>
<td>TS</td>
</tr>
<tr>
<td>16</td>
<td>Tue</td>
<td>3/5</td>
<td>Potentially inappropriate prescribing</td>
<td>TS</td>
</tr>
<tr>
<td>17</td>
<td>Thu</td>
<td>3/7</td>
<td>The opioid epidemic</td>
<td>Nab Dasgupta</td>
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<td>Thu</td>
<td>3/7</td>
<td><strong>Agreed upon term paper topic</strong></td>
<td></td>
</tr>
</tbody>
</table>

Spring Break (3/9 – 3/17)
<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Date</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Tue</td>
<td>3/19</td>
<td>Methods review</td>
<td>TS</td>
</tr>
<tr>
<td>19</td>
<td>Thu</td>
<td>3/21</td>
<td>Practical lessons for a successful career in pharmacoepidemiology</td>
<td>Nancy Dreyer</td>
</tr>
<tr>
<td>20</td>
<td>Tue</td>
<td>3/26</td>
<td>Paper Presentation I</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Thu</td>
<td>3/28</td>
<td>Paper Presentations II</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Tue</td>
<td>4/2</td>
<td>Medications in pregnancy</td>
<td>Sara Ephross</td>
</tr>
<tr>
<td>23</td>
<td>Thu</td>
<td>4/4</td>
<td>Methodology</td>
<td>Richard Wyss</td>
</tr>
<tr>
<td>Mo</td>
<td>4/8</td>
<td></td>
<td><strong>Term paper due</strong></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Tue</td>
<td>4/9</td>
<td>Pragmatic trials</td>
<td>Michael Kappelman</td>
</tr>
<tr>
<td>25</td>
<td>Thu</td>
<td>4/11</td>
<td>Propensity score trimming</td>
<td>Robert Glynn</td>
</tr>
<tr>
<td>26</td>
<td>Tue</td>
<td>4/16</td>
<td>Self-controlled designs</td>
<td>Jesper Hallas</td>
</tr>
<tr>
<td>27</td>
<td>Thu</td>
<td>4/18</td>
<td>Single arm studies with external comparator</td>
<td>Christina Mack</td>
</tr>
<tr>
<td>28</td>
<td>Tue</td>
<td>4/23</td>
<td>Antidepressants and suicide</td>
<td>Matt Miller</td>
</tr>
<tr>
<td>29</td>
<td>Thu</td>
<td>4/25</td>
<td>Wrap-up</td>
<td>TS</td>
</tr>
</tbody>
</table>
Lesson 1: What is pharmacoepidemiology?

Required readings:
- None

Suggested readings:

Lesson 2: Sources of data for PE

Required readings:
- Strom BL. Overview of automated databases in pharmacoepidemiology. Pharmacoepidemiology, 5th edition, chapter 11

Suggested readings:

Lesson 3: Drug, outcome, and comorbidity data

Required readings:
• Suzanne L. West, Brian L. Strom, Charles Poole. Validity of Pharmacoepidemiologic Drug and Diagnosis Data. Pharmacoepidemiology, 5th edition, chapter 41


Suggested readings:


Lesson 4: Methodologic challenges in PE

• Confounding (by indication, frailty)
• Selection bias

Required readings:


Suggested readings:


• Schneeweiss S, Patrick AR, Sturmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and
comparison with randomized trial results. Medical Care. 2007 45: 10(2):131-142.


Lesson 5: Study Design Solutions
- New user design
- Active comparators

Required readings:

- Journal club article: Chang HY, Singh S, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients With Type 2 Diabetes. JAMA Intern Med. 2018 Sep 1;178(9):1190-1198.

Suggested readings:


Lesson 6: Risk periods
- First treatment carried forward
- As treated
- Induction, carry-over, lag periods

Required readings:


Suggested readings:


• Stampfer MJ. ITT for observational data: worst of both worlds? Epidemiology. 2008 Nov;19(6):783-4

Lesson 7: Propensity scores

Required readings:


Suggested readings:


• Stürmer T, Wyss R; Glynn RJ; Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. Journal of Internal Medicine 2014;275(6):570-80.

• Stürmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially
different estimates compared with conventional multivariable methods. Journal of Clinical Epidemiology 2006;59:437-47.

Lesson 8: Propensity scores cont.'d & disease risk scores

Required readings:


Suggested readings:


Lesson 9: Non-uniform treatment effects

Required readings:


- Journal club article: Yoshida K, Hernández-Díaz Sonia, Solomon DH, Jackson JW, Gagne JJ, Glynn RJ, Franklin JM., Jessica M. Matching Weights to Simultaneously Compare Three Treatment Groups:

Suggested readings:


Lesson 10: Instrumental variables

Required readings:


Suggested readings:


Lesson 11: Validation studies
Required readings:


Suggested readings:


- Brunelli SM, Gagne JJ, Huybrechts KF, Wang SV, Patrick AR, Rothman KJ, Seeger JD. Estimation using all available covariate


**Lesson 12: Crystal ball PE, immortal time bias, immeasurable time bias**

**Required readings:**


- Journal club article: Suissa S. Lower Risk of Death With SGLT2 Inhibitors in Observational Studies: Real or Bias. Diabetes Care 2018;41:6–10

**Suggested readings:**


**Lesson 13: Adherence and Persistence**

**Required readings:**


Suggested readings:


Lesson 14: Patients treated contrary to prediction

Required readings:


Suggested Readings:


Lesson 15: Variability in treatments & variable selection (including hdPS)

Required readings:


Suggested readings:

Lesson 16: Potentially inappropriate prescribing

Required readings:


Suggested readings:


Lesson 17 The opioid epidemic

Required readings:

Lesson 18 Methods review

Required readings:


Lesson 19 Practical lessons for a successful career in pharmacoepidemiology

Required readings:


Lesson 20 Paper Presentation I

Lesson 21 Paper Presentation II

Lesson 22 Medications in Pregnancy

Required readings:


Lesson 23 Methodology

Required readings:

• Journal club article: Richardson DB, Keil AP, Kinlaw AC, Cole SR. Marginal Structural Models for Risk or Prevalence Ratios for a Point
Lesson 24 Pragmatic trials

Required readings:


Suggested readings:


Lesson 25 Propensity score trimming

Required readings:


Lesson 26 Self-controlled designs

Required readings:


Lesson 27 Single arm studies with external comparator

Required readings:

- Journal club article:

Lesson 28 Antidepressants and suicide
Required readings:


Lesson 29 Wrap-up

Required readings: