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 12 – April 27, 2017
Tuesday, Thursday, 2:00 – 3:15
Room: Rm MGG 1305

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: draft PE book chapter review/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 on a draft PE book chapter, 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 will be drawn from a PE textbook that is currently drafted by the lead instructor and from the literature.

**Expectations:**

- All students are expected to read required articles and PE book chapters (all provided on Sakai) before class and to participate actively in class discussions.
- Students leading the discussion on a book chapter are expected to
  - As a team of 3 (alphabetically assigned)
    - Meet to discuss chapter before class to structure the in-class discussion
    - Provide a written 1-page team consensus document with high level comments
    - Lead the 30’ discussion in class
  - Each team member separately
    - Proofreads the Word version
      - Edits (e.g., typos, language, references)
      - Specific comments (e.g., missing here is XYZ)
    - Using the track changes mode
  - Both consensus and individual annotated chapters are due 5 calendar days after class
- All students are expected to write a term paper on a pharmacoepidemiologic topic (see below).

**Grading:**

30%: Class participation
30%: Presentation and discussion of book chapter
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.

**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 (2010 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 3/1 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 3/9). 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 4/10 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 drugs 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”].

Honor code: Each student is required, and therefore assumed, to be familiar with the Instrument of Student Governance and to abide by it. The Instrument
is available at http://instrument.unc.edu/. Other information on the UNC Honor System is at http://honor.unc.edu/.

Appendix A to the Instrument states that each student is expected to “Sign a pledge on all graded academic work certifying that no unauthorized assistance has been received or given in the completion of the work.” It is the student’s responsibility to know this pledge, write it down, and sign it on all graded academic work, whether or not a designated space is provided for it on the assignment or exam. The instructors reserve the right to deduct points without advance warning for failure to comply with this requirement.

Basic definition of “unauthorized assistance” for the graded assignments consists of using any unreferenced materials or computer programs. If you have any specific questions about what constitutes “unauthorized assistance” while completing an assignment please ask the instructor.

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 2015 (Lead-Instructor: Jennifer Lund). Students are also encouraged to come to the Pharmacoepidemiology Seminar on Mondays, 3:30-4:30.

Textbook: No textbook other than the draft chapters of the PE book prepared by the instructor.

Selection of and some comments on existing pharmacoepidemiology textbooks:

Available in the library for this course. This is a reasonably priced textbook providing a good overview, including overview of often used healthcare databases.


Much extended scope compared with prior versions (see below). Good examples. PERM from now on. ~$200, but I saw one on sale for $99. Currently revised for next edition.


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


No textbook but comprehensive behind-the-scenes look at issues that affect everyone: our shortage of data comparing the worth of similar drugs for the same condition; alarming lapses in the detection of lethal side effects; the underuse of life-saving medications; lavish marketing campaigns that influence what doctors prescribe; and the resulting upward spiral of costs that places vital drugs beyond the reach of many Americans. Hardcover ~$20, Paperback ~$10

Selection of epidemiology textbooks


The bible in its 3rd edition. Still the best and cheaper than many others. A must have for anyone interested in non-experimental population research. ~$80


A simple (but neither simplistic nor outdated as so many others) overview of the concepts that are the underpinnings of epidemiology, so that a coherent picture of epidemiology thinking emerges. The emphasis is not on statistics, formulas, or computation, but on epidemiologic principles and concepts*. ~$40
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<td>• Confounding (by indication, frailty)</td>
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<td>• Selection bias (healthy initiator, sick stopper, healthy user)</td>
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<td>Study Design Solutions</td>
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<td>• New user design</td>
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<td>Risk periods</td>
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<td>• First treatment carried forward</td>
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<td>• As treated</td>
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<td>• Induction, carry-over, lag periods</td>
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<td>Instrumental variables</td>
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<td>Crystal ball PE, immortal time bias, immeasurable time bias</td>
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<td>3/1</td>
<td><strong>Term paper proposal</strong></td>
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<td>Thu</td>
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<td><strong>Agreed upon term paper topic</strong></td>
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<td>We</td>
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<td>Harry Guess Memorial Lecture: Susana Perez-Gutthann</td>
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<td>28</td>
<td>Tue</td>
<td>4/25</td>
<td>Guest speaker: Nancy Dreyer (Outcomes/Quintiles): TBD</td>
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<td>29</td>
<td>Thu</td>
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Potential list of guest speakers to present in EPID 765

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<tr>
<th>Name</th>
<th>Suggested topic</th>
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<td>Kevin Haynes (HealthCore)</td>
<td>Distributed databases</td>
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<td>Darren Toh</td>
<td>Automated PE (sentinel)</td>
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<td>Bob Glynn</td>
<td>Treatment equipoise</td>
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<td>Susana Perez-Gutthann</td>
<td>TBD</td>
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<td>Sara Ephross</td>
<td>Medications in pregnancy</td>
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<td>Michael Kappelman</td>
<td>Large simple trials to study drug effects</td>
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<td>Elizabeth Andrews</td>
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<td>Matt Miller</td>
<td>SSRIs and injury</td>
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<td>Tobias Gerhard</td>
<td>Mental health PE</td>
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<td>Christina Mack</td>
<td>Emerging therapies</td>
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<td>Hugh Tilson</td>
<td>History of PE/ISPE</td>
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<td>Cindy Girman</td>
<td>Methodological work within Pharma</td>
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<td>Mary Beth Richey</td>
<td>Drug/device application process</td>
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<td>Art Sedrakyan</td>
<td>Device epidemiology</td>
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<td>Sudha Raman</td>
<td>Self-controlled designs</td>
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<td>Nabarun Dasgupta</td>
<td>Opioid crisis</td>
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<td>Annie McNeill</td>
<td>Diabetes treatments</td>
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<td>Nancy Dreyer</td>
<td>TBD</td>
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### Student Presentations

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<th>Students</th>
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<td>Intro</td>
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<td>Danielle Chun&lt;br&gt;Ashley Cole&lt;br&gt;Thibaut Davy</td>
<td>Nonexperimental</td>
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<tr>
<td>1/26</td>
<td>Mathew Dixon&lt;br&gt;Matina Gaggi&lt;br&gt;Patrick Healy</td>
<td>New user</td>
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<td>1/31</td>
<td>Ryan Hickson&lt;br&gt;Damon Houghton&lt;br&gt;Shelley Jazowski</td>
<td>Risk periods</td>
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<tr>
<td>2/2</td>
<td>Emily Learner&lt;br&gt;Jennifer Lee&lt;br&gt;Sophie Mayer</td>
<td>PS</td>
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<tr>
<td>2/7</td>
<td>Aaron Mitchell&lt;br&gt;Jason Rotter&lt;br&gt;Shahar Shmuel</td>
<td>DRS</td>
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<td>Amanda Tapia&lt;br&gt;Tengteng Wang&lt;br&gt;Tiansheng Wang</td>
<td>Non-uniform effects</td>
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<td>2/21</td>
<td>Michael Webster-Clark&lt;br&gt;Yuzhi Xi&lt;br&gt;Jeff Yang</td>
<td>Immortal</td>
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<tr>
<td>2/28</td>
<td>Kanecia Zimmerman&lt;br&gt;Mackenzie Herzog&lt;br&gt;Raquel Masegu&lt;br&gt;Troels Munch</td>
<td>Pts treated contrary to prediction</td>
</tr>
</tbody>
</table>
Lesson 1: What is pharmacoepidemiology?

Required readings:
- None

Suggested readings:

Student presentation:
- None

Lesson 2: Sources of data for PE

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

Suggested readings:

Student presentation:
- None

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:


Student presentation:

• PE book Intro

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.
Student presentation:

- PE book Nonexperimental

**Lesson 5: Study Design Solutions**

- New user design
- Active comparators

Required readings:


Suggested readings:


Student presentation:

- New user

**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

Student presentation:
• Risk periods

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.

Student presentation:

• Propensity scores

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

Required readings:


Suggested readings:

• Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. AJE 2011.
• Hansen BB. The prognostic analogue of the propensity score. Biometrika 2008; 95(2): 481-488.

Student presentation:

• Disease risk scores

Lesson 9: Non-uniform treatment effects

Required readings:


Suggested readings:


Student presentation:

• Non-uniform treatment effects

Lesson 10: Instrumental variables

Required readings:


Suggested readings:


Student presentation:

None

Lesson 11: Validation studies

Required readings:


Suggested readings:


Student presentation:

• None

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

Required readings:


Suggested readings:


Student presentation:

• Immortal

Lesson 13: Adherence and Persistence

Required readings:


Suggested readings:

• Brookhart MA, Patrick AR, Schneeweiss S, Avorn J, Dormuth C, Shrank W, van Wijk BL, Cadarette SM, Canning CF, Solomon DH. Physician follow-up and provider continuity are associated with long-


Student presentation:

- None

**Lesson 14: Patients treated contrary to prediction**

**Required readings:**


**Suggested Readings:**


Student presentation:

- Patients treated contrary to prediction

**Variability in treatments & variable selection (including hdPS)**

**Required readings:**


**Suggested readings:**

Student presentation:

- None

Lesson 15: Potentially inappropriate prescribing

Required readings:


Suggested readings:


Student presentation:

- None