New onset diabetes in Covid-19

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Game plan

- Consider some new reports, including a meta-analysis, that examine the risk of glycemic abnormalities and/or diabetes after Covid-19 illness
- Remind you of some physiology and pathophysiology that you once had studied and mastered
- Review some new news releases and MMWR short reports if time permits
- Pass one or more quizzes at the end

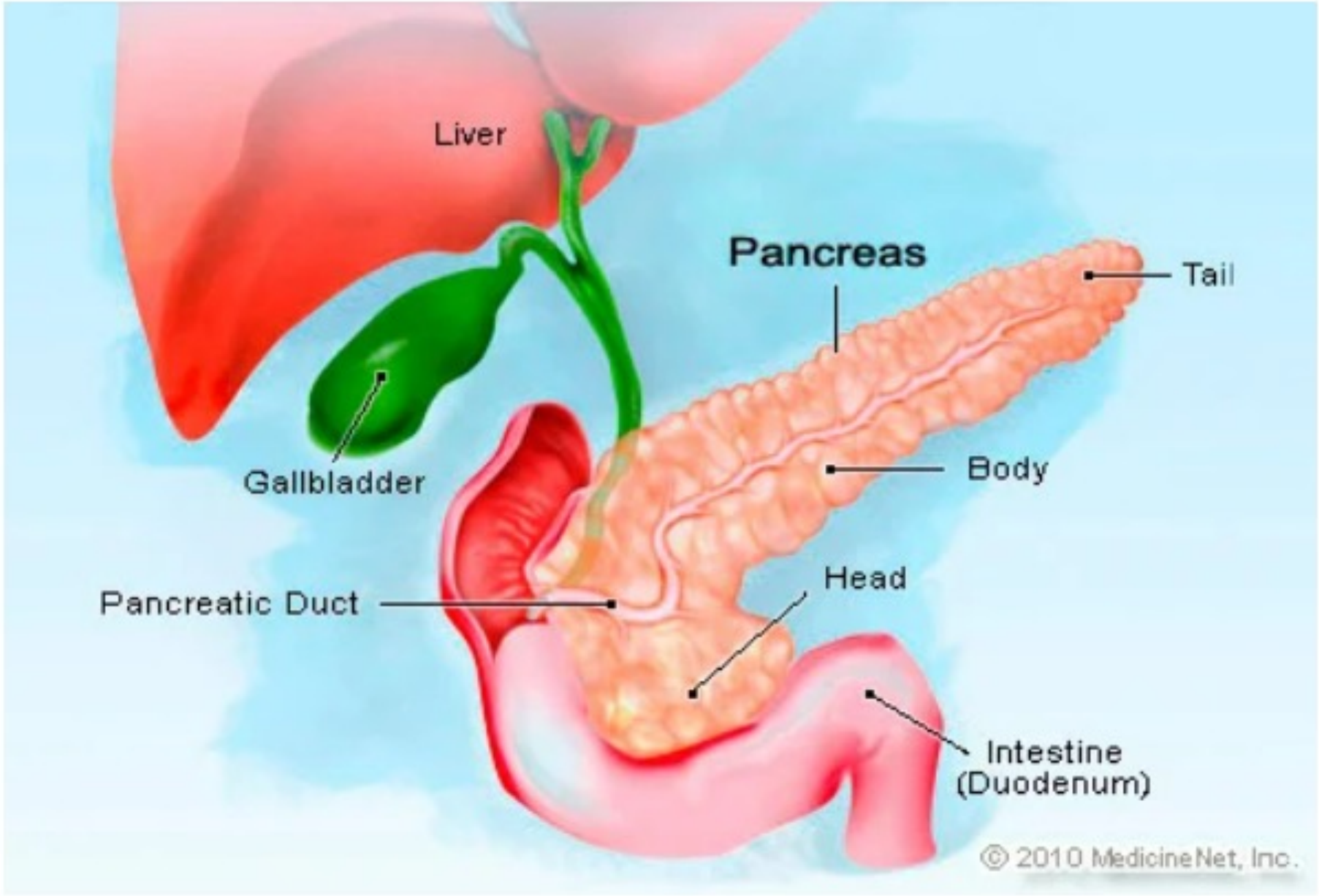
- *Thanks to one of our audience members for suggesting the topic as it might relate to Indian country*

Objectives

- Cite evidence related to risk of diabetes or longer-term abnormalities of glycemic control, post Covid-19
- Summarize key findings on meta-analysis of retrospective cohorts of Covid-19 patients and new onset diabetes
- Explain possible mechanisms that may be at work in development of glycemic control abnormalities post Covid-19 (the pathophysiology)

Take home messages for today

- Bidirectional relationship between Covid-19 and diabetes
- New onset diabetes and severe metabolic complications of pre-existing diabetes have been observed in Covid-19 patients (some say 'commonly observed')
- Diabetic ketoacidosis and hyperosmolarity, requiring high doses of insulin, pose management challenges in Covid-19 patients
- A registry has been established (CoviDIAB) to address multiple questions related to Covid-19 and long term dysregulation of blood sugar


Liver
Pancreas
Tail
Gallbladder
Body
Head
Pancreatic Duct
Intestine
(Duodenum)
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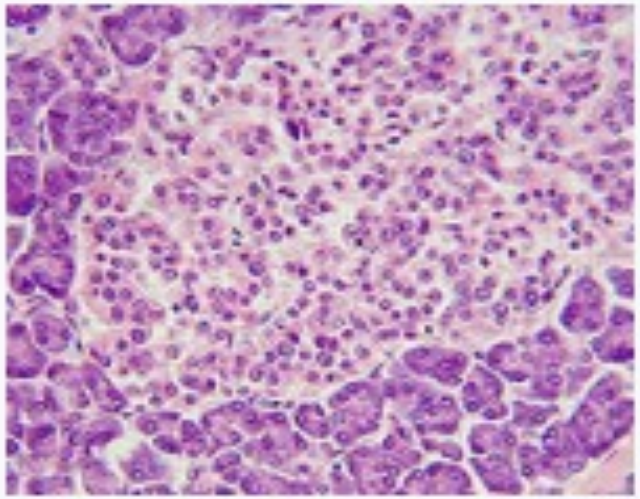
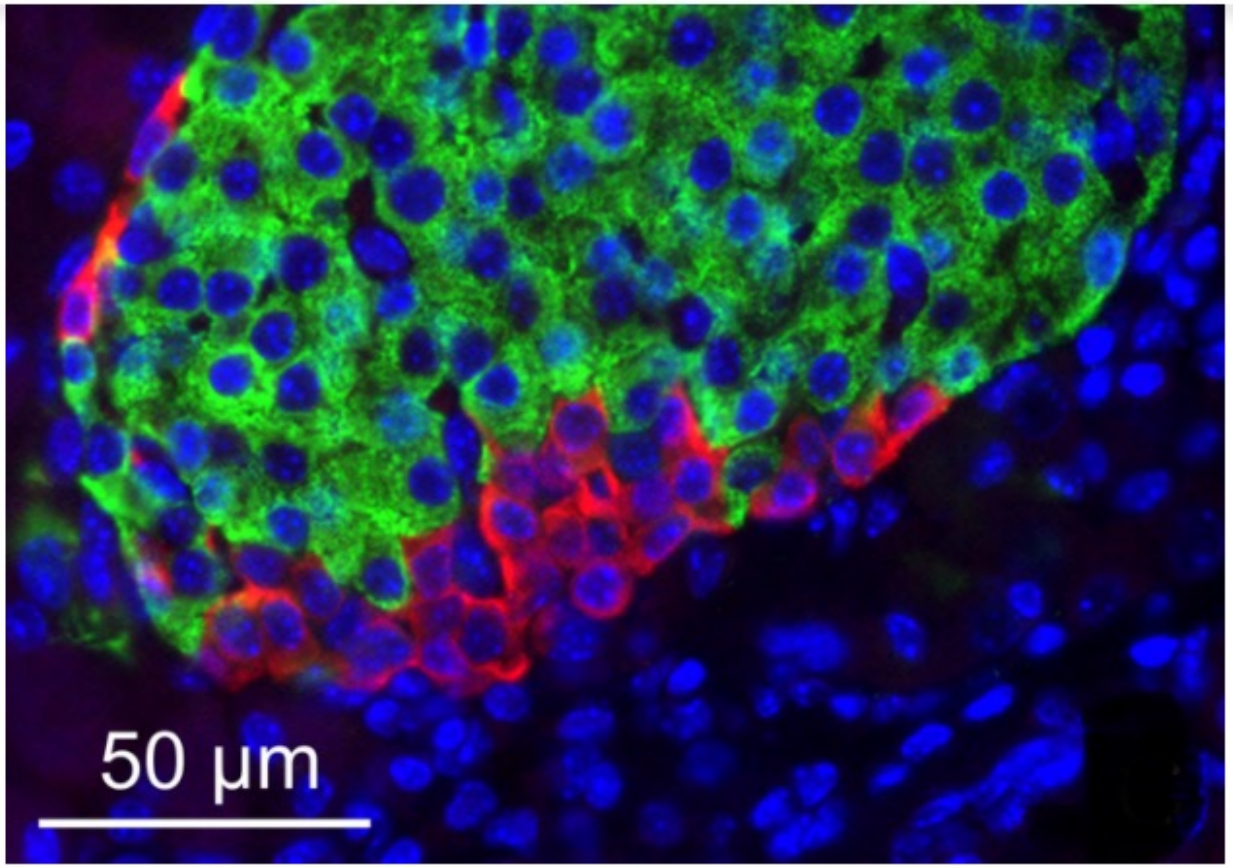


Pancreatic islets, the lighter tissue among the darker, acinar pancreatic tissue, hemalum-eosin stain.



Islet of Langerhans. Cells of the Islet of Langerhans in the pancreas produce insulin and glucagon, hormones that work together to regulate the levels of blood sugar in the body. This image captures two main cell types as revealed by immunohistochemistry, a special staining process. Beta cells (green) produce insulin and alpha cells (red) produce glucagon. The nuclei of the cells is shown in blue. Image courtesy of Ge Li/Waterland lab/*Environmental Epigenetics,* 2019.

Reminder from school days

- Pancreas has both an exocrine and endocrine role in normal physiology
- Different cell types in this organ have different functions—beta cells produce insulin and alpha islet cells produce glucagon
- Endocrine components (insulin, proinsulin, glucagon) can be measured with various tests
- The physiology and pathophysiology of this organ is VERY complex and glucose regulation is difficult to fully understand
- Re: glucose control, many factors are at work, including insulin production, glucagon, epinephrine, norepinephrine, acetylcholine, insulin resistance, post-insulin receptor factors…and more!

More reminders of stuff you know already…

- Insulin is a peptide hormone produced by beta cells of the pancreatic islets—the main anabolic hormone of the body
- Regulates metabolism of carbohydrates, fats and protein by promoting the absorption of glucose from the blood into liver, fat, and skeletal muscle
- In these tissues, glucose is converted into glycogen or fats
- It promotes conversion of small molecules in the blood into large molecules inside the cells
- Low insulin levels, on the opposite part of the spectrum, promote widespread catabolism—especially fat reserves

Background

- Precedents for viral cause of abnormal glucose metabolism and ketosis-prone diabetes, including other coronaviruses that bind to ACE-2 receptors
- Higher occurrence of fasting glycemia and acute-onset diabetes among SARS pneumonia patients
- SARS-CoV-2 binds to ACE-2 receptors in key organs and tissues, including pancreatic beta cells (that produce insulin)
- Case reports of new onset diabetes and severe complications in pre-existing diabetes in Covid-19 patients
- Observations support the hypothesis of a potential diabetogenic effect of Covid-19…but do the abnormalities persist?

Background

- SARS can enter and damage the pancreatic beta cells, resulting in decreased production of insulin or defective insulin production
- SARS may also injure the beta cells by triggering a host of pro-inflammatory cytokines or by enhancing autoimmunity in genetically predisposed people
- Binding of SARS to ACE2 receptors in multiple other tissues (like skeletal muscle, liver, adipose) may impair responses to insulin, and thus, may also be important in the pathogenesis of DM as a result of infection (easier version: insulin cannot get glucose in these tissues easily and 'do its job', thus high levels or high concentrations of insulin may be needed to drive glucose into the cells)
- Cytokines induced by SARS infection can also affect insulin receptor signaling….so, this is complicated!

Background, cntd

- Relevant questions that warrant answers:

1. if abnormal glucose metabolism is observed in a Covid patient or series of patients, how long will it last and how severe might it become?

2. what is the risk of (permanent) DM in Covid-19 patients, and/or risk of DKA?

3. is the type of diabetes more like type 1 of type 2? Or a different type?

4. among those with pre-existing diabetes, does Covid-19 change the natural history of the disease?

5. How long does a Covid-19 survivor with glucose metabolic abnormalities need to be closely followed for control?

Binding of SARS CoV to its receptor damages islets and causes DM

- Interesting analogy between SARS and SARS-CoV-2 re: pancreatic islet cells
- Case-control approach (in part), comparing biomarkers among SARS patients and sibling controls without SARS in China
- 20/39 patients were hyperglycemic during hospitalization
- 6/39 had DM at discharge from hospital
- After three years, only 2/39 had DM
- Authors concluded that SARS may damage islets and cause acute insulin dependent diabetes, with long-term effects in a small proportion of patients

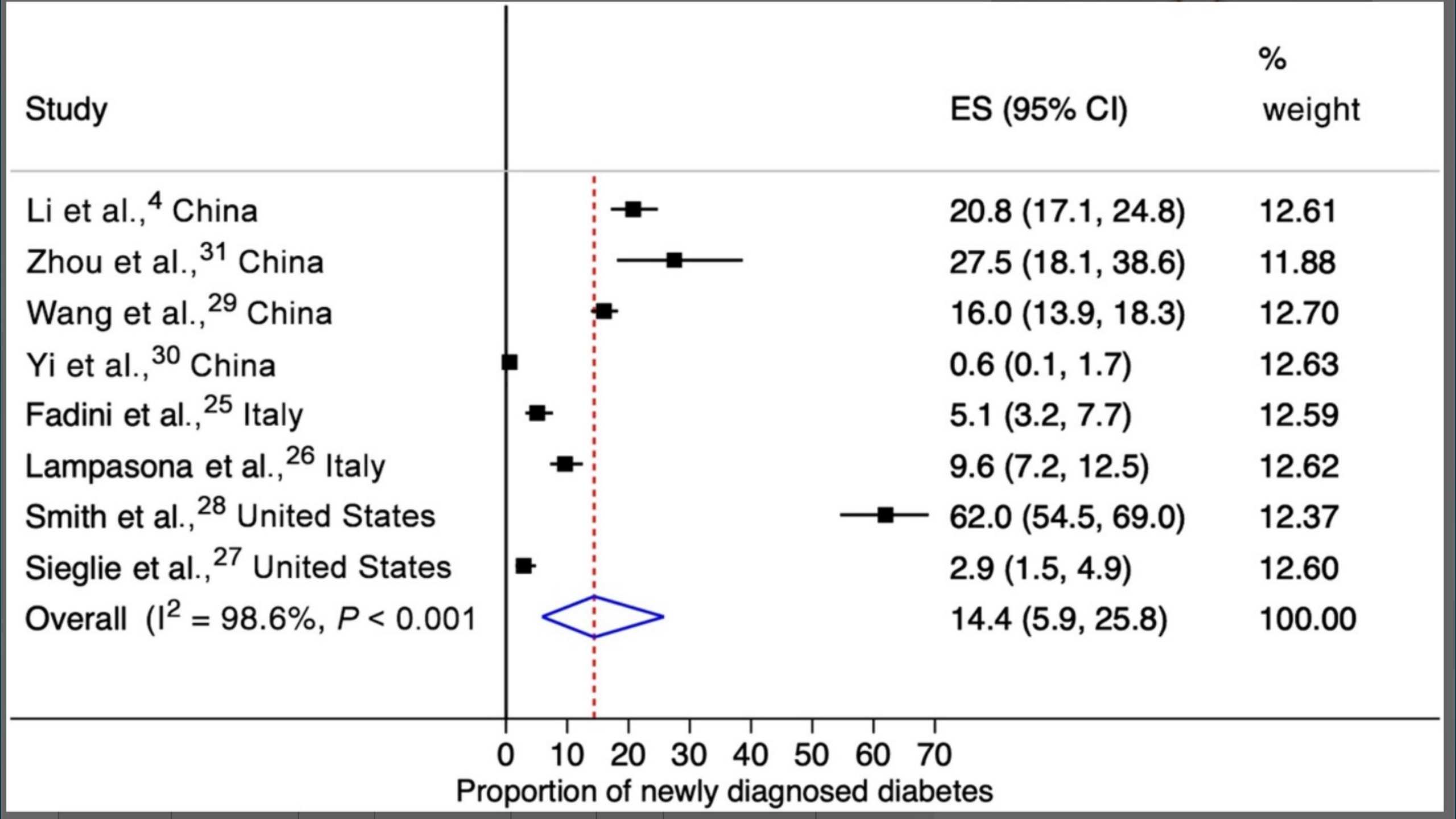
Systematic review and meta-analysis of DM in Covid-19

- Included observational studies that provided data on the % of Covid-19 patients with newly-diagnosed DM
- Search terms new-onset diabetes, newly diagnosed diabetes, incident diabetes, transient hyperglycemia, in conjunction with covid-19.
- Total of 148 studies in multiple languages, included 8 studies in analysis that satisfied the criteria for inclusion
- All retrospective cohort studies during first 5 months of pandemic
- Quality studies: fair to good
- All studies were hospital-based

Key findings

- 3700 patients included in the 8 studies
- Pooled % with newly diagnosed DM: 14.4%

- See following table/figure


Study
ES (95% CI)
% weight
Li et al.,[4] China
20.8 (17.1, 24.8)
12.61
Zhou et al.,[31] China
27.5 (18.1, 38.6)
11.88
Wang et al.,[29] China
16.0 (13.9, 18.3)
12.70
Yi et al.,[30] China
0.6 (0.1, 1.7)
12.63
Fadini et al.,[25] Italy
5.1 (3.2, 7.7)
12.59
Lampasona et al.,[26] Italy
9.6 (7.2, 12.5)
12.62
Smith et al.,[28] United States
62.0 (54.5, 69.0)
12.37
Sieglie et al.,[27] United States
2.9 (1.5, 4.9)
12.60
Overall (I^2 = 98.6%, P < 0.001
14.4 (5.9, 25.8)
100.00
0
10
20
30
40
50
60
70
Proportion of newly diagnosed diabetes

Limitations

- Few studies met the criteria for inclusion
- All were hospital based, half from China (limits generalizability)…would be instructive to include community-based cases with milder disease
- Number of studies was small, and as meta-analyses go, the total number of included patients was small

Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection

Laura Montefusco[1,16], Moufida Ben Nasr[2,3,16], Francesca D'Addio[2,16], Cristian Loretelli[2], Antonio Rossi[1], Ida Pastore[1], Giuseppe Daniele[4], Ahmed Abdelsalam[2], Anna Maestroni[2], Marco Dell'Acqua[2,5], Elio Ippolito[2], Emma Assi[2], Vera Usuelli[2], Andy Joe Seelam[2], Roberta Maria Fiorina[2], Enrica Chebat[1], Paola Morpurgo[1], Maria Elena Lunati[1], Andrea Mario Bolla[1], Giovanna Finzi[6], Reza Abdi[7], Joseph V. Bonventre[7], Stefano Rusconi[8], Agostino Riva[8], Domenico Corradi[9], Pierachille Santus[10,11], Manuela Nebuloni[12,13], Franco Folli[14], Gian Vincenzo Zuccotti[1,15], Massimo Galli[8] and Paolo Fiorina[1,2,3] ✉

Acute and long-term disruption of glycometabolic control after SARS

- 551 Covid patients hospitalized in Italy
- Multiple serum studies for a panel of biomarkers, in addition to blood glucose values
- Simple analyses determined percent of hospitalized patients with hyperglycemia
- Assessed glycometabolic markers of control, including insulin resistance
- Followed patients up to 6 months post d/c
- Publication date June 2020 so likely less delta variant-associated cases than would currently be the case.

Methods, continued

- Authors had access to very sophisticated tools to measure Beta cell function, insulin resistance, secretome levels (about 12 different cytokines), and a host of other biomarkers
- short-term, cohort study-type repeated measures of key biomarkers on subsets of patients
- longer-term assessments of a subset of patients, including controls who did not have Covid-19

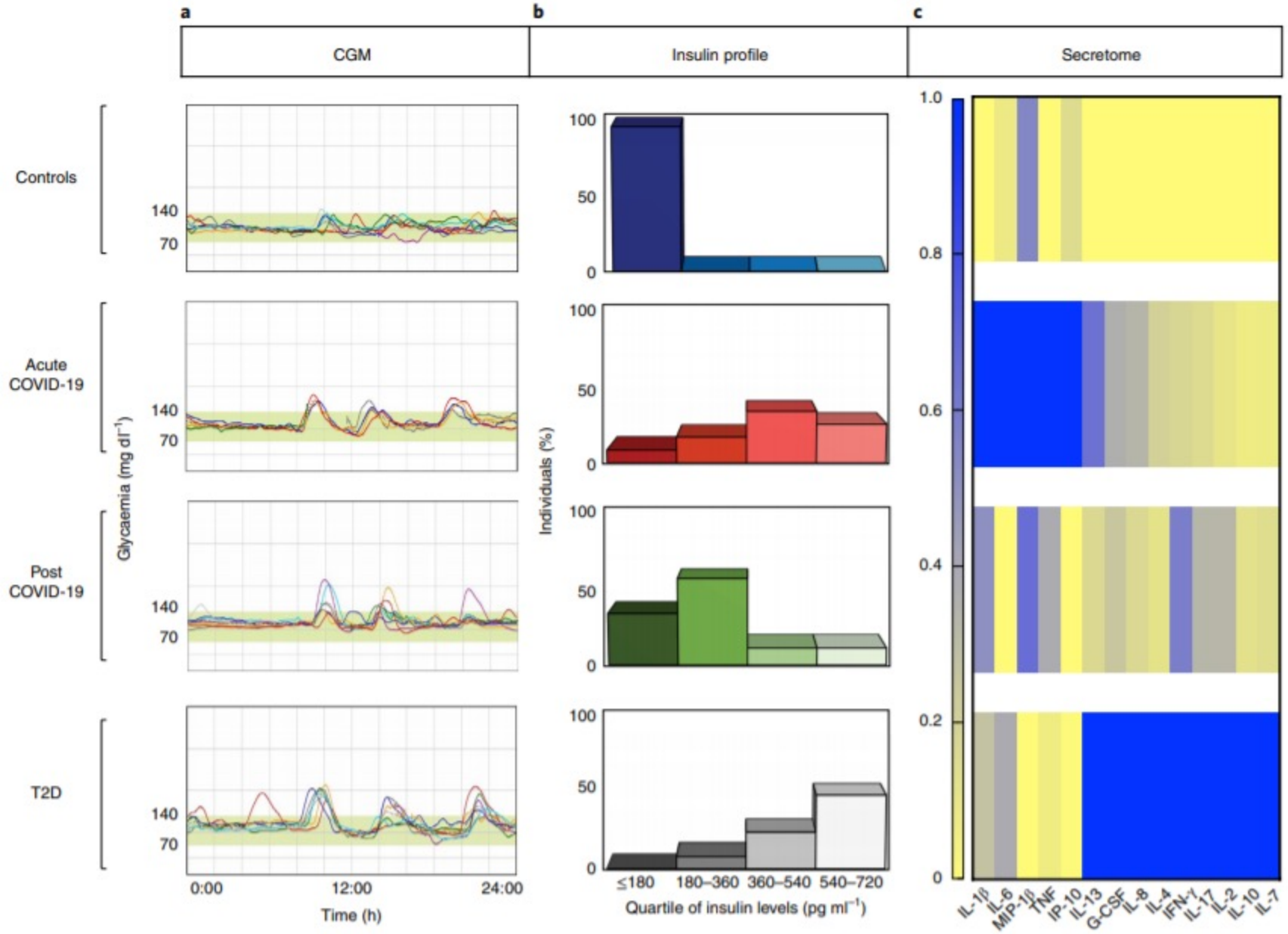
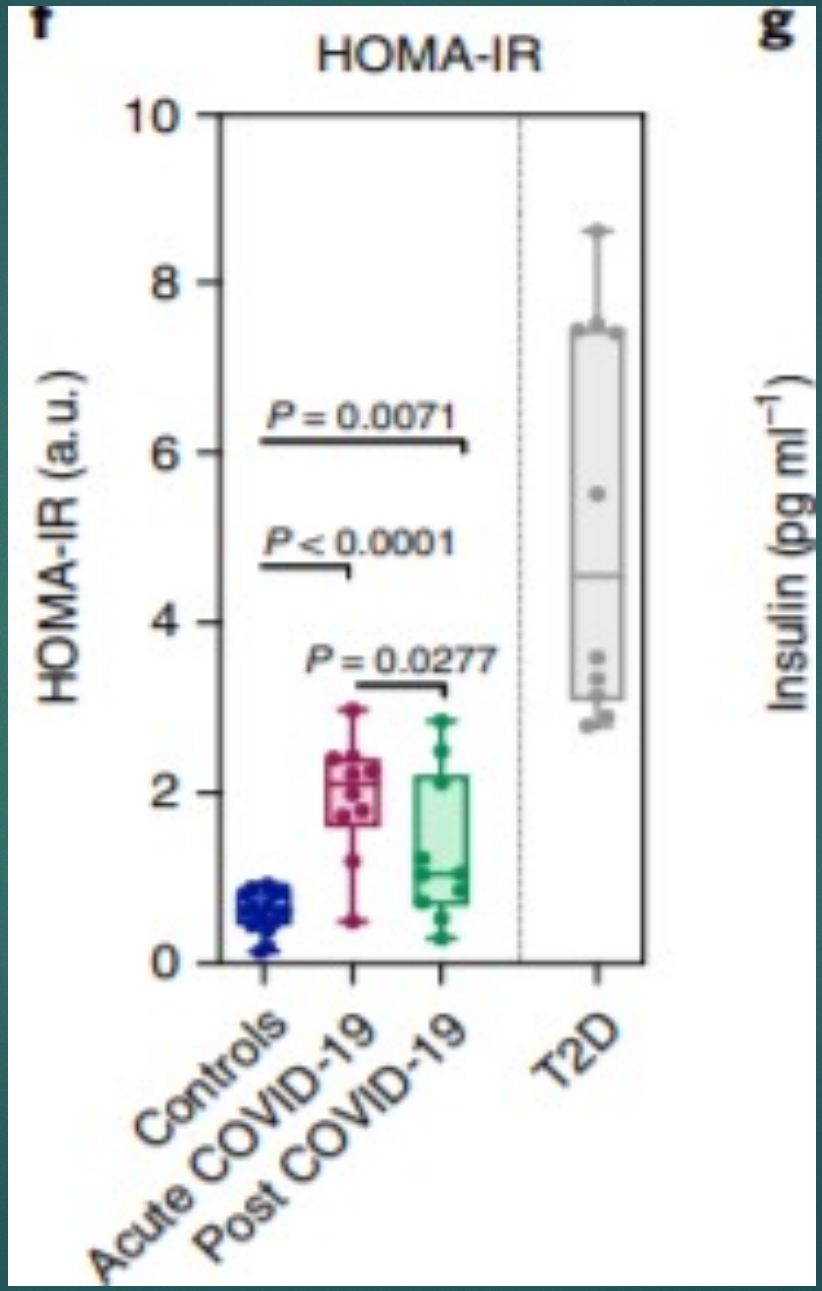
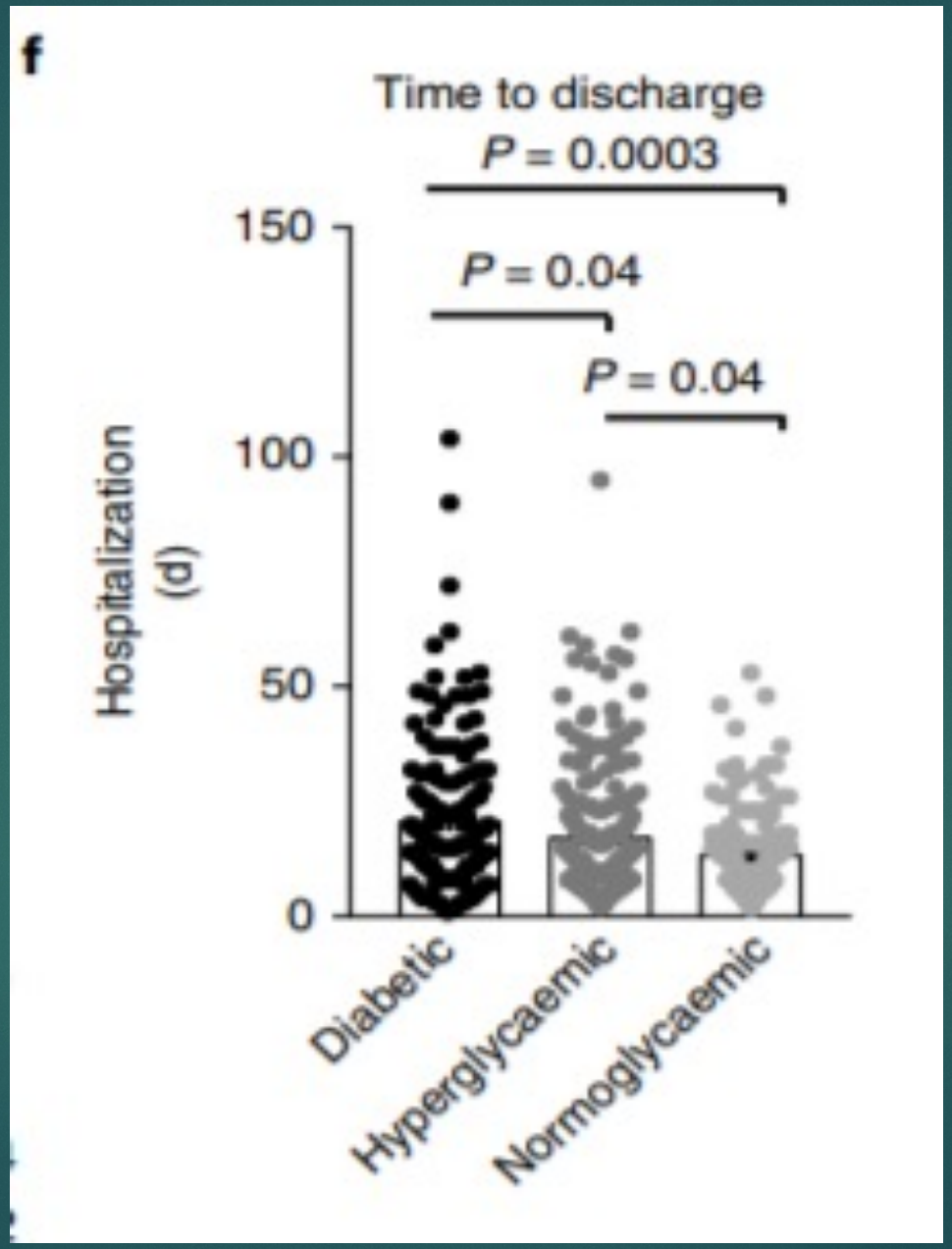
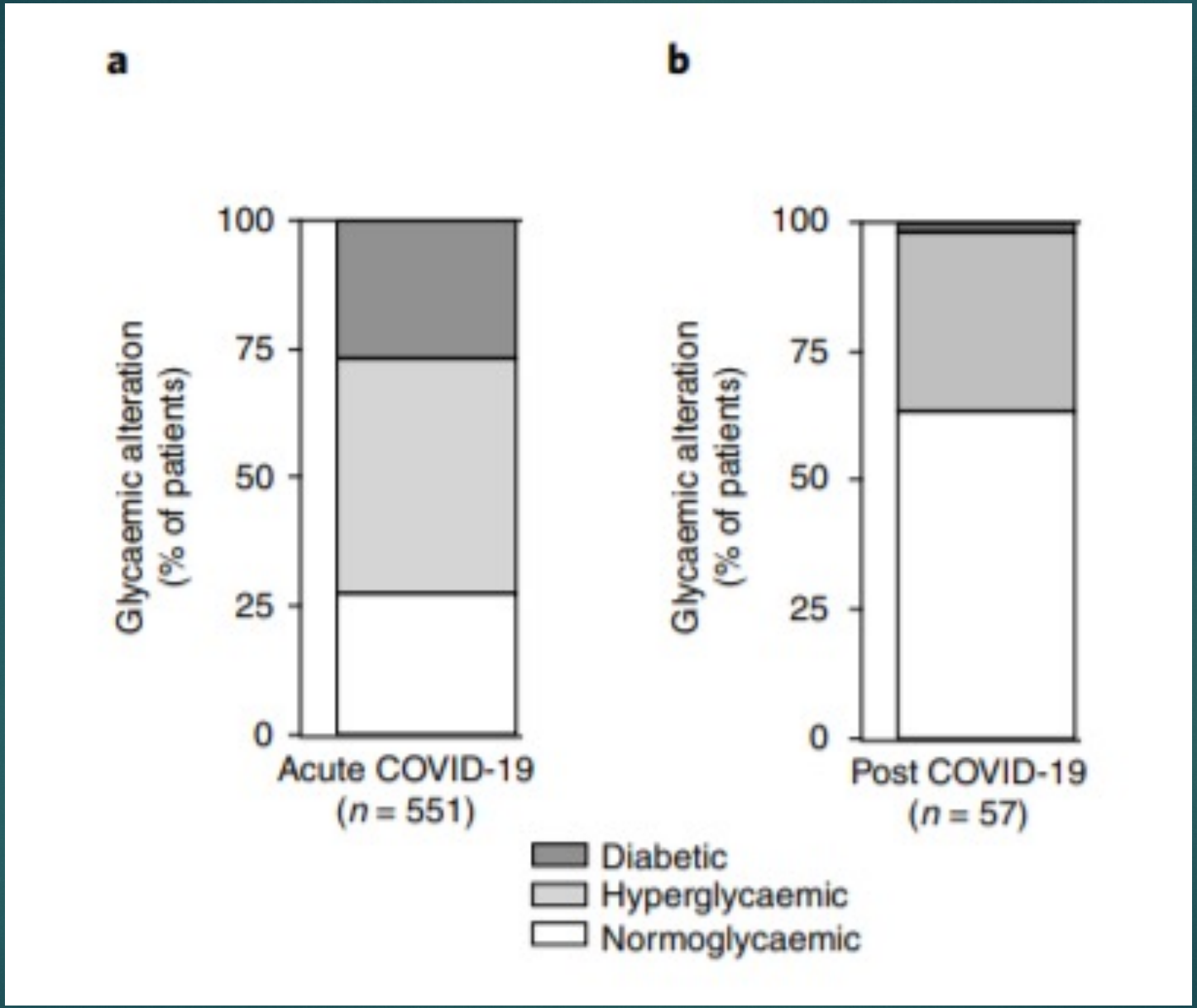
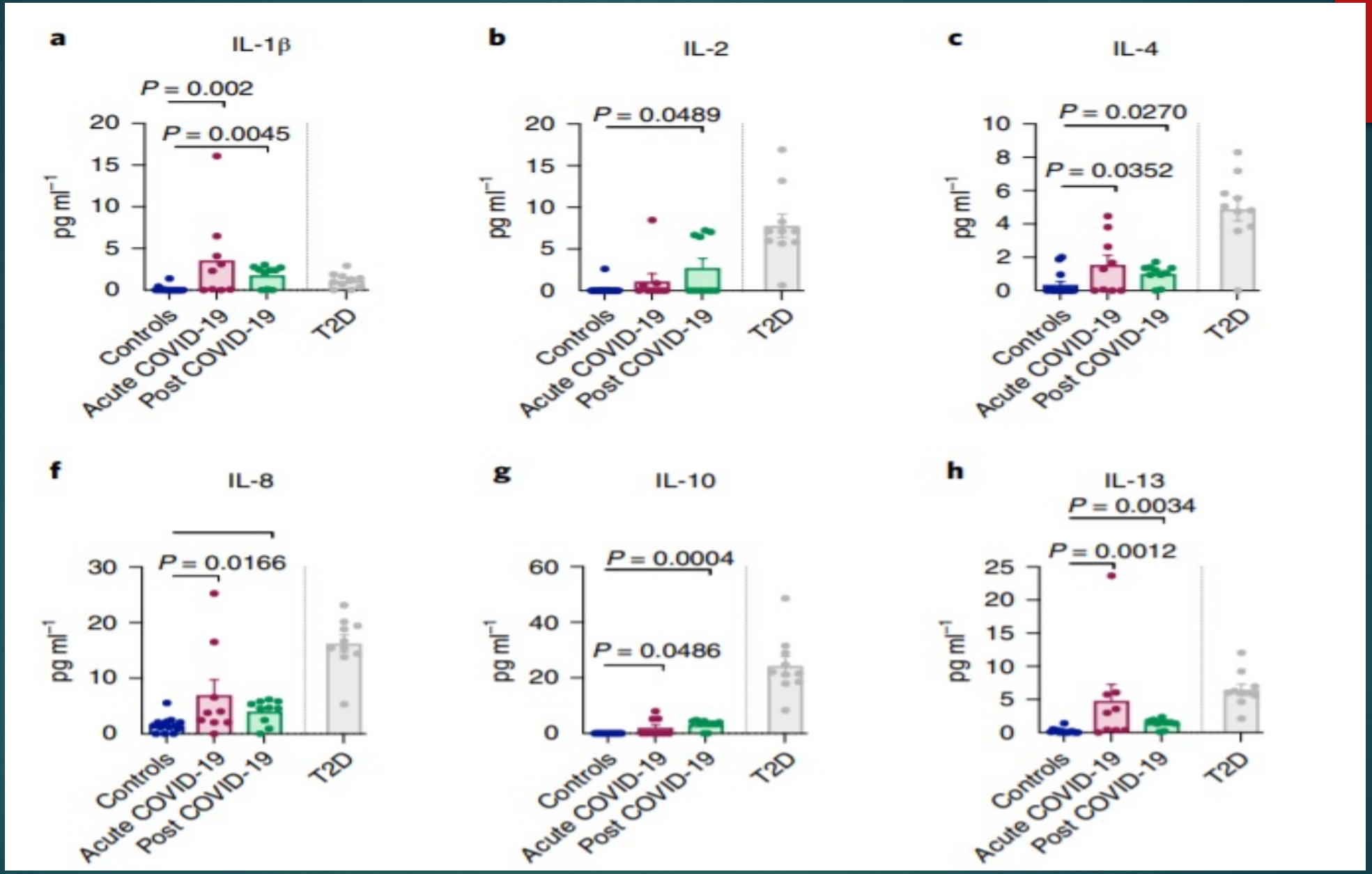


Fig. 5 | Evidence of glycometabolic, hormonal and secretome abnormalities in patients with COVID-19. a–c, Comparative schematic/analysis showing abnormalities in CGM (**a**), insulin levels (**b**) and secretome profile (**c**) in patients with COVID-19 (acute COVID-19), in those who recovered from COVID-19 (post COVID-19) and in patients with T2D, demonstrating similarities with those found in patients with T2D. Data in **c** are represented as colour-coded


f
HOMA-IR
g
HOMA-IR (a.u.)
Insulin (pg ml^{-1})
10
8
6
4
2
0
P = 0.0071
P < 0.0001
P = 0.0277
Controls
Acute COVID-19
Post COVID-19
T2D


f
Time to discharge
P = 0.0003
P = 0.04
P = 0.04
Hospitalization (d)
150
100
50
0
Diabetic
Hyperglycaemic
Normoglycaemic


a
b
100
75
50
25
0
Glycaemic alteration
(% of patients)
Acute COVID-19
(n = 551)
Post COVID-19
(n = 57)
Diabetic
Hyperglycaemic
Normoglycaemic


a
IL-1β
P = 0.002
P = 0.0045
pg ml−1
20
15
10
5
0
Controls
Acute COVID-19
Post COVID-19
T2D
b
IL-2
P = 0.0489
pg ml−1
20
15
10
5
0
Controls
Acute COVID-19
Post COVID-19
T2D
c
IL-4
P = 0.0270
P = 0.0352
pg ml−1
10
8
6
4
2
0
Controls
Acute COVID-19
Post COVID-19
T2D
f
IL-8
P = 0.0166
pg ml−1
30
20
10
0
Controls
Acute COVID-19
Post COVID-19
T2D
g
IL-10
P = 0.0004
P = 0.0486
pg ml−1
60
40
20
0
Controls
Acute COVID-19
Post COVID-19
T2D
h
IL-13
P = 0.0034
P = 0.0012
pg ml−1
25
20
15
10
5
0
Controls
Acute COVID-19
Post COVID-19
T2D

Potential limitations of this study

- A strong retrospective cohort component
- Each of the lab assessments has limitations related to test characteristics (sensitivity, specificity)
- Very small numbers of patients in continuous glucose monitoring studies, and other spin-off studies
- The 30 graphs and tables included took a long time to digest, not usually considered a limitation!

Take away messages from this study

- Cytokine profiles in Covid-19 patients and survivors of Covid are markedly different from that of controls
- Observed hyperglycemia, insulin resistance, and beta cell dysfunction might be due the proinflammatory 'milieu' initiated by cytokine storm
- SARS Cov-2 induces insulin resistance and disrupts proper beta cell function, which can result in clinically evident hyperglycemia detectable even after Covid acute illness
- Abnormalities in glucose control exist months after disease recovery
- Larger cohort/s could help sort out biomarkers more completely

authors' comments:

- Our data suggest that Covid-19-associated new onset hyperglycemia may predispose patients to long term hyperglycemia, worse clinical outcomes and clinical scores, prolonged hospital stays, and higher demand for oxygen support or positive pressure ventilation

- They observed increased mortality among those with established AND new onset diabetes (Hazard ratio compared to normoglycemic patients 2.16; for new onset hyperglycemia, HR 2.05)

CoviDIAB registry

- Global registry focused on this intersection of acute and chronic diseases
- King's College in London is home base
- Goals: establish the extent and phenotype of new onset DM that is defined by hyperglycemia, confirmed Covid-19, a negative history of DM, and a history of a normal hemoglobin level
- Hope to gain insights into better management of these patients

Quiz

- How would you counsel your own patients, or relay information to clinicians who manage the patients where you live…about their risk of DM post covid? Do we have enough information now to provide wise guidance?
- What might you tell patients or their families about survival rates or risks in the face of new onset hyperglycemia?
- What type of study or studies can you suggest that would address key unanswered questions about DM post Covid-19?

References

- Montefusco, et al. Acute and long term disruption of glycometabolic control after SARS-CoV-2 infection. Nature Metabolism 25 May 2021
- Starling. How Covid-19 disrupts glycometabolic control. Metabolism 17 (448) 2021.
- Sathish et al. Proportion of newly diagnosed DM in Covid-19 patients (meta-analysis). Diabetes, Obesity, and Metabolism Vol 23 (3), 2020.
- Rubino et al. New-onset diabetes in Covid-19. NEJM 383, August 20, 2020.
- Yang et al. Binding of SARS CoV to its receptor damages islets and causes acute DM. Acta Diabetol 47; 2010.

A few snippets for your consideration

- OPB and Science blurbs on boosters
- Recent MMWR ‘short stories’

The vaccination drive has been slower than the Biden administration had hoped for. At the same time, the variant is spreading aggressively through unvaccinated communities and also causing an increasing number of "breakthrough infections" of fully inoculated people.

Studies show the vaccine remains highly protective against severe COVID-19, but results from Israel released last month suggest its effect wanes. Its effectiveness against symptomatic infection peaked at 96% two months after study participants got their second dose. Four months later, it was down to 90%. By six months, it was about 84%.

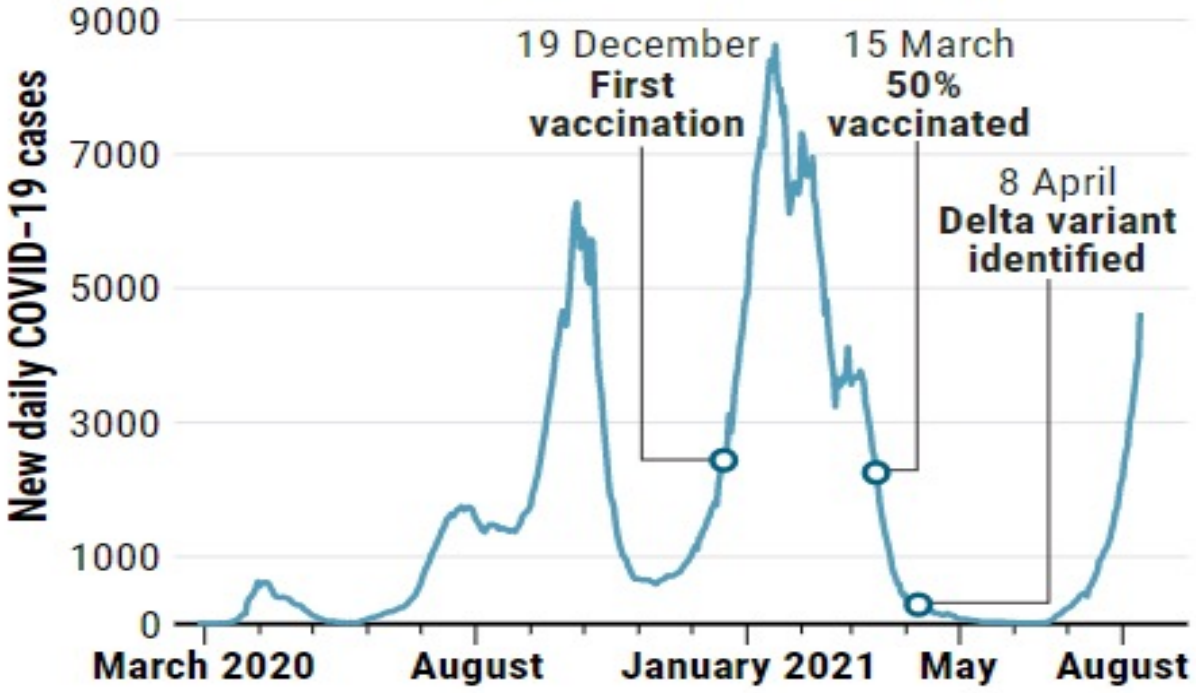
Medical staff at a COVID-19 isolation unit in Ashkelon, Israel, last week. Officials worry a steep surge in cases will soon fill Israeli hospitals. GIL COHEN MAGEN/XINHUA/GETTY IMAGES

A grim warning from Israel: Vaccination blunts, but does not defeat Delta

By Meredith Wadman | Aug. 16, 2021 , 6:55 PM

Israel's sobering setback

Israel, which has led the world in launching vaccinations and in data gathering, is confronting a surge of COVID-19 cases that officials expect to push hospitals to the brink. Nearly 60% of gravely ill patients are fully vaccinated.



(GRAPHIC) K. FRANKLIN/*SCIENCE*; (DATA) H. RITCHIE *ET AL.*,

- Israel embarking on third dose of Pfizer vaccine for all age-eligible people (as of today, ages 50 years and above)
- Their plan is countered by experts on opposite side of the fence…see UCSF Medical grand rounds on Covid, Dr. Del Rio presentation
- Promoting booster doses will fit into the anti-vax arguments, from a sociologic perspective….and could dampen efforts to get all eligible people to be vaccinated

Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination — Kentucky, May–June 2021

Weekly / August 13, 2021 / 70(32);1081-1083

On August 6, 2021, this report was posted online as an MMWR *Early Release.*

Alyson M. Cavanaugh, DPT, PhD[1,2]; Kevin B. Spicer, MD, PhD[2,3]; Douglas Thoroughman, PhD[2,4]; Connor Glick, MS[2]; Kathleen Winter, PhD[2,5] (View author affiliations)

Kentucky study, MMWR

- Kentucky immunization registry
- Case-control approach
- All records included were of Covid patients
- Case: a person with reinfection after a 5 month period from first infection
- Control: former Covid patient not reinfected
- Exposure of interest: partial, fully, or no vaccine post initial infection
- Control for relevant confounders

TABLE 2. Association of SARS-CoV-2 reinfection* with COVID-19 vaccination status — Kentucky, May–June 2021

Vaccination status	No. (%)		OR (95% CI)†
	Case-patients	Control participants	
Not vaccinated	179 (72.8)	284 (57.7)	2.34 (1.58–3.47)
Partially vaccinated¶	17 (6.9)	39 (7.9)	1.56 (0.81–3.01)
Fully vaccinated§	50 (20.3)	169 (34.3)	Ref
Total	**246 (100)**	**492 (100)**	—

Abbreviations: CI = confidence interval; NAAT = nucleic acid amplification test; OR = odds ratio; Ref = referent group.

*All case-patients (reinfected) and control participants (not reinfected) had previous SARS-CoV-2 infection documented by positive NAAT or antigen test results during March–December 2020. Reinfection was defined as receipt of positive NAAT or antigen test results during May 1–June 30, 2021.

Effectiveness of COVID-19 Vaccines in Preventing Hospitalization Among Adults Aged ≥65 Years — COVID-NET, 13 States, February–April 2021

Weekly / August 13, 2021 / 70(32);1088-1093

On August 6, 2021, this report was posted online as an MMWR *Early Release.*

FIGURE 2. Estimates of vaccine effectiveness in preventing COVID-19–associated hospitalization among patients aged ≥65 years for the COVID-NET catchment area, by vaccine product and age group using the screening method — COVID-NET, 13 states,* February 1–April 30, 2021†

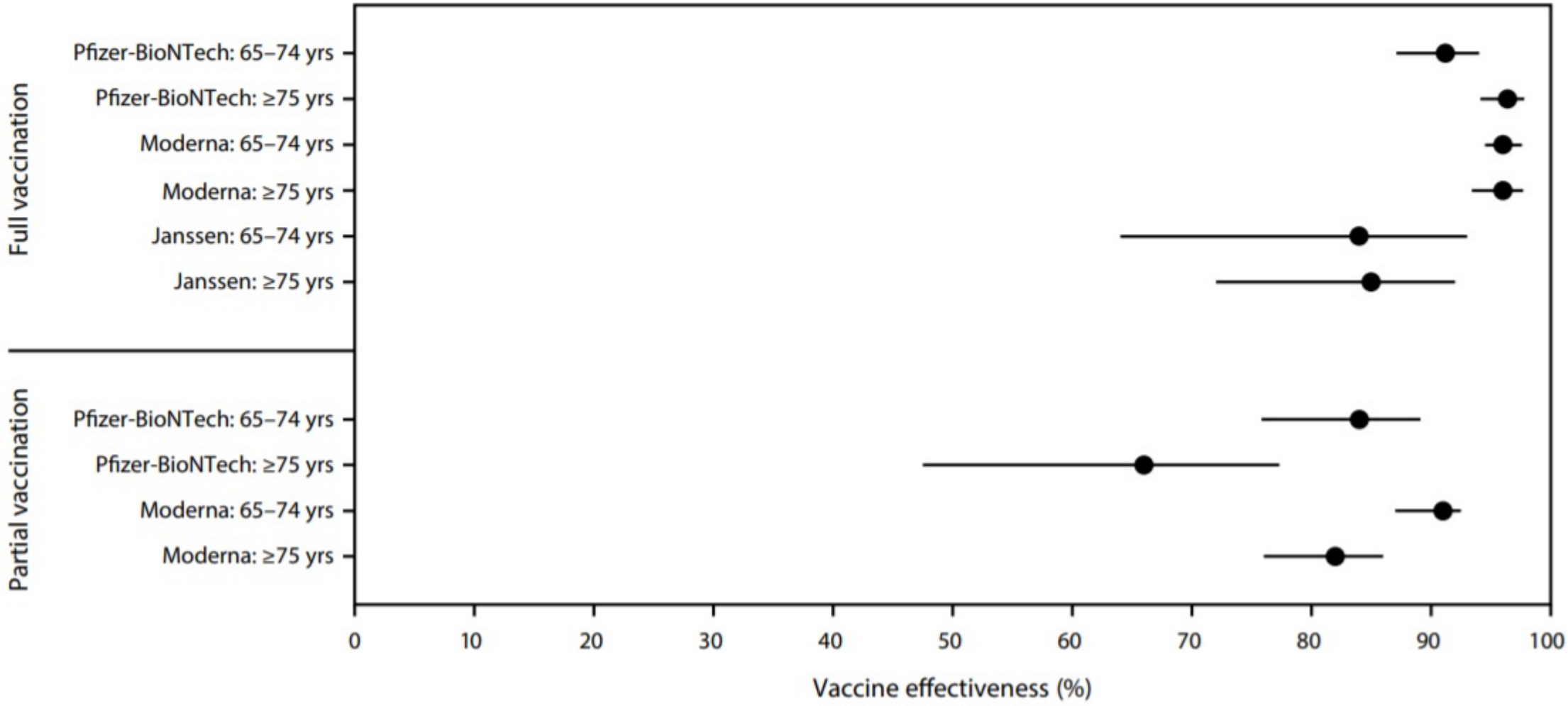
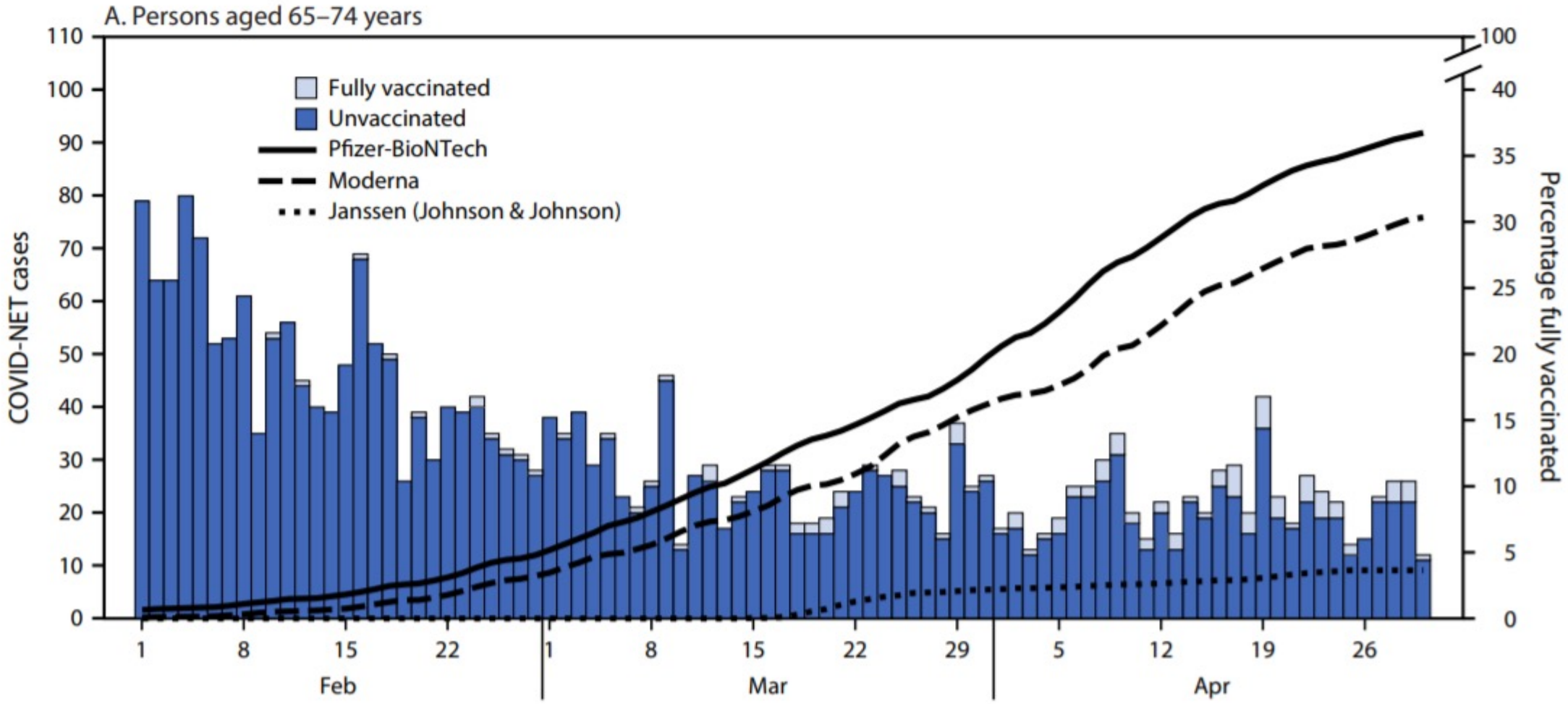


FIGURE 1. COVID-NET* cases and full vaccination coverage among persons aged 65–74 years (A) and persons aged ≥75 years (B) — 13 states, February 1–April 30, 2021



Let's briefly reconsider Sydney outbreak June 19, 2021

- 30 people attended a birthday party, 6 vaccinated, 24 unvaccinated people
- One of the party-goers apparently exposed to SARS-CoV-2 that had come into the country via international flight crew (the limo driver who transported that airline crew had a central role in epidemic)
- All unvaccinated persons got delta variant, none of the vaccinated
- Household transmission occurred rapidly from the 24 infected persons, with fast transmission into other types of venues
- Sydney locked down, as well as other provinces and jurisdictions
- New infections in Melbourne, another major population center, traced via Sydney

From a public health standpoint, how can these health-conscious birthday partiers be so happy looking? Pick all of the correct answers:

- 1. they were all vaccinated and knew that about each other
- 2. they all had antigen test negative results the day before
- 3. they had all been isolated for one week before party, save for the antigen test
- 4. they know to not blow out the candles
- 5. they only blow into devices that contain and isolate any viruses, for those who just cannot stand to not blow out candles
- 6. they correctly wear their N 95 masks except to have this picture taken
- 7. same as above with physical distancing
- 8. they will all go back outside after foto op
- 9. the party will only last 15 minutes
- 10. the party was not in Australia